American Heart Journal

An international publication for the study of the circulation

GEORGE E BURCH M D
Editor

NICHOLAS P DePASQUALE M D
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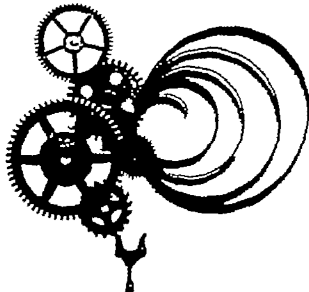
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Contents

Editorial

Clinical communications

continued on page 3



like clockwork

the smooth interaction of
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amounts makes Plexonal the
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Contents *continued*

Experimental and laboratory reports

Case report

Review

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Contents *continued*

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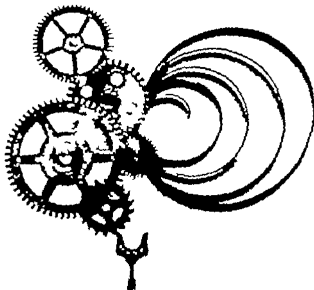
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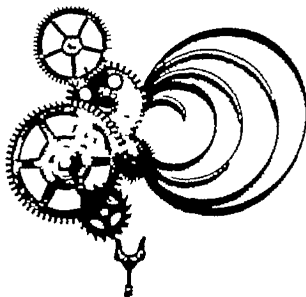
AUGUST 1964

Contents

continued on page 3



continued on page 5



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Contents *continued*

Appraisal and reappraisal of cardiac therapy

Annotations

Letter to the Editor

Book reviews

Announcements

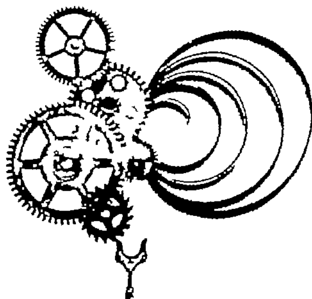
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American Heart Journal

SEPTEMBER 1964

Contents

continued on page 3



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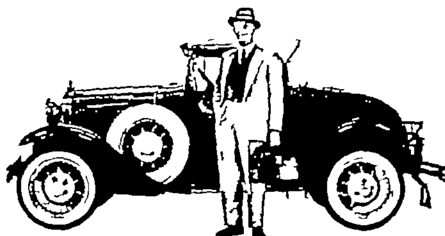
Contents *continued*

Experimental and laboratory reports

Case reports

Review

continued on page



One thing two generations of physicians have in common .



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In treating coronary occlusion it is essential to relieve the pain as soon as possible We have u ed Dilaudid extensively and have found it to be a reliable analgesic which produces fewer unpleasant and dangerous side effects than morphine

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Contents *continued*

Fundamentals of clinical cardiology

Appraisal and reappraisal of cardiac therapy

Annotations

Book reviews

Announcements

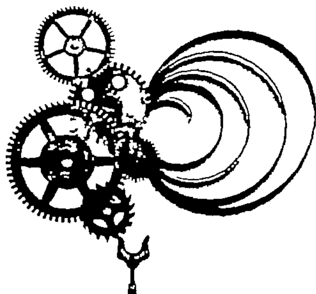
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American Heart Journal

OCTOBER 1964

Contents

continued on page 3





SANDOZ

Contents *continued*

Experimental and laboratory reports

Case reports

Clinical pathologic conference

continued on page 2





One thing two generations of physicians have in common

Dilaudid (hydromorphone) – still unmatched for analgesic action

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Contents *continued*

Fundamentals of clinical cardiology

Appraisal and reappraisal of cardiac therapy

Annotations

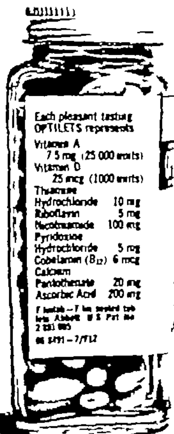
Book reviews

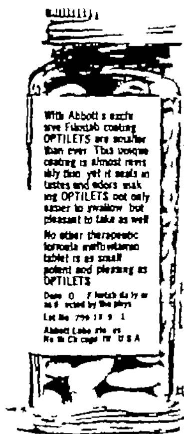
Announcements

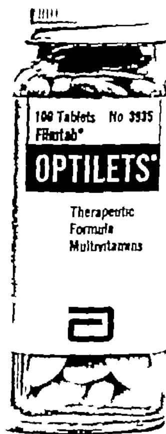
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American Heart Journal

NOVEMBER 1964

Contents

continued on page 3

PLEXONAL

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SANDOZ

Contents *continued*

Experimental and laboratory reports

Case reports

Review

continued on page 5

Contents *continued*

Fundamentals of clinical cardiology

Appraisal and reappraisal of cardiac therapy

Annotations

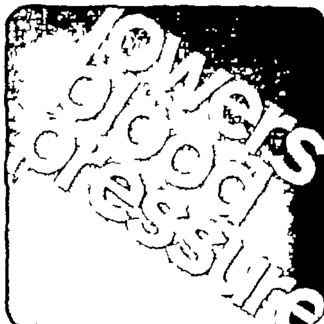
Book reviews

Announcements

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American Heart Journal

DECEMBER 1964

Contents

continued on page 3

PLEXONAL

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Contents *continued*

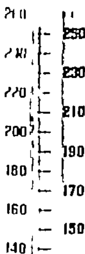
continued on page 8

Contents *continued*

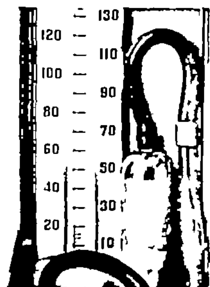
Book review

Index

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American Heart Journal

July, 1964 Volume 68 Number 1

Editorial

The mortality rate from heart disease

Maurice Campbell, O.B.E.
London, England

The large increase in the death rate from heart disease since about 1924 and especially in that from coronary heart disease is one of the most striking features of recent medical statistics. In the first[1] of two papers in the *British Medical Journal* I discussed the changes that have taken place, and in the second paper I brought forward evidence that the increase in the death rate from heart disease as a whole may be due entirely to the older age of the population and that the much greater increase in the death rate from coronary heart disease is due mainly to increasing medical knowledge and more accurate diagnosis.

I summarized the crude annual death rates per million persons living, as reported by the Registrar General. All the figures discussed are for men and women combined, although some of the trends discussed would have been even more striking for the men alone. The death rates from all diseases of the circulatory system, from all diseases of the heart, and from vascular lesions of the central nervous system are considered from 1876 shortly, and from 1891 through 1960 more fully.

The death rates from the main subdivisions of diseases of the heart also are summarized. Changes in the Registrar General's classification are discussed but do not seem to be an important cause of the findings. Changes in medical views and knowledge seem to be more important and explain the rise in registered deaths from valvular disease of the heart up until 1917 and the fall especially after 1931, and much, if not all, of the rise in deaths from coronary heart disease since 1924.

The death rate from *all diseases of the heart* changed very little from 1876 to 1920, and probably from 1850. About 1924 it began increasing rapidly, and rose from 100 to 263 per cent by 1952, since when it has shown some signs of settling at the higher level.

The recorded death rate from *coronary heart disease* started increasing about the same time in geometrical rather than in arithmetical progression. This rise is still continuing, although largely after 1940 and entirely after 1951 it must be due to a change in diagnosis, since it is entirely balanced by a fall in the deaths attributed to other myocardial disease. The original level was so low that the deaths from coronary heart disease were not of much arithmetical importance until about 1940.

The death rate from *cerebrovascular lesions* behaved in much the same way as that from all diseases of the heart and the

From the Cardiac Department, Guy's Hospital, and the Institute of Cardiology, London, England.

Received for publication [illegible] 21, 1963.

increase was of the same order but rather less—from 100 to 220 per cent instead of from 100 to 263 per cent

In the second paper I explained what I think to be the main cause of this large increase in deaths from all forms of heart disease and presumably of those from cerebrovascular accidents also Because nothing has been done to reduce the risks of dying from most diseases of the heart after middle age and so much has been done to reduce the risk of dying from infectious diseases mainly in infancy and childhood it is inevitable that the death rate from diseases of the heart must increase these two changes have not been connected so closely as they should have been because of the interval of 40 years between them

The *death rate from all causes* changed only slightly from 1838 when the statistics of the Registrar General started until 1880 and over all this period it averaged 21 7 per 1 000 persons living After 1880 it fell somewhat and was about 18 7 per 1 000 for the years 1881 1895 It then fell much more rapidly until 1925 when it was 10 7 per 1 000—a little less than half of the level maintained from 1838 to 1880 Since 1926 it has fallen only slightly and is not likely to fall much until something more can be done about deaths from heart disease and cancer Indeed sometime it is likely to rise when there is no longer a rising birth rate to offset the increasing age of the population

Most of the lives saved were those of infants and children dying from infective gastroenteritis and other infectious diseases and those of young adults dying from tuberculosis I calculated their average age at death as between 16 and 20 years I used the latter figure but in retrospect think that the former is probably more accurate The mean age at death of subjects dying from heart disease has been increasing from 59 years in 1910 to 73 years in 1959 so that in the earlier years of our period there would be an interval of 40 years between the times when many subjects who might have died from infectious diseases did in fact die from heart disease

On the assumption (1) that the fall in the death rate was mainly from 1885 to 1925 (because the fall was gradual and small in 1880 1895) and (2) that those who ultimately died from heart disease did so 40 years later than they would have from infectious diseases a large increase in the death rate from heart disease should have been expected from 1925 to 1965 Making these assumptions but distributing the new deaths from heart disease more widely at various ages (instead of taking the mean age) I have calculated the expected death rate from all diseases of the heart from 1880 It rose very slowly until 1917 rather more quickly from then until 1937 and much more quickly from 1927 to 1973 and then slowly but hardly significantly until 1990 The close agreement of these calculated figures with the recorded death rate from 1880 to 1960 suggests that all of the increase in the recorded death rate from diseases of the heart including coronary heart disease could be due to this cause I consider that the increasing age of the population caused by the lives saved because of the better control of infectious diseases is the main if not the only reason for the large increase in the deaths from all heart disease since about 1924

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Intrinsicoid atrial P-wave deflections in unipolar intracardiac electrograms

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It has always been difficult during cardiac catheterization to define accurately the borders of the left atrium and often impossible without elaborate sampling of blood to tell exactly when a catheter has entered this chamber. Since the introduction of intracardiac electrography in 1945[1] it has been repeatedly stated[2-7] that the right and left atrium can be distinguished by studying the morphology of the P waves recorded inside the heart with an electrode catheter and comparing them with those in a simultaneously recorded scalar lead. It has been said that because the sinoatrial node is in the right atrium, right atrial activation takes place earlier than left, and that for this reason the intrinsicoid deflections of right atrial P waves coincide with the ascending limb and the intrinsicoid deflections of the left atrial P waves with the descending limb of the P wave in standard leads.

To test the truth of this suggestion a study has been made of the intracardiac electrograms recorded routinely during cardiac catheterization of some 500 patients with acquired or congenital heart disease. In more than 100 cases electrograms of both the left and right sides of the heart were available for comparison. The left heart had in all cases been catheterized either through an atrial septal defect or via a valve-patent foramen ovale. Electrode catheters manufactured by the United States Catheter and Instrument Corporation were used to record unipolar intracardiac electrograms which, unless otherwise stated, were standardized at a deflection of 1 millivolt per centimeter. In each case a scalar electrocardiographic Lead II and a pressure pulse were also recorded. The three signals were photographed simultaneously on 6-inch Kodak R.P. 30 paper at 25 mm. per second with a New Electronic Products Ltd. multichannel recorder. In the illustrations the standard lead is at the top, the intracardiac lead in the middle, and the pressure pulse at the bottom. Cardiac catheterization was from the groin, and withdrawal tracings are therefore in that direction. Where necessary, the intracardiac complexes have been emphasized with black ink to make them clearly visible.

The nomenclature P_Q, P_{QR}, P_{QRS}, P_R, P_S, and P_T suggested by Hecht[8] in 1946 has been adopted to designate the individual components of the intracardiac P waves. The term "intrinsicoid" has been chosen to denote the atrial deflection which starts at the top of the P_R wave or, in the absence of a positive deflection, the downstroke of P_{QS}. It has been used because the electrode, although inside the heart, is not in contact with the myocardium, and these deflections are therefore not truly intrinsic. Some of them, however, are of such high voltage and so rapidly inscribed that they must reflect a close proximity to the atrial wall. For

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Fig 6 A withdrawal from the left to the right atrium through a small defect high in the inter atrial septum in which the tip started far out to the left pressed against the lateral wall of the left atrium and produced atrial contact currents On withdrawal it crosses through the mid left atrial cavity and as it rises to pass through the septum the intrinsicoid P wave deflections become progressively earlier since the electrode is gradually getting closer to the sinoatrial node Once through the defect however it moves down toward the inferior vena cava in the direction of the withdrawal and the deflections again become later ($^1/_2$ mv = 1 cm)

trated in the long withdrawal tracing seen in Fig 6 Here the tip of the catheter has been pressed initially against the lateral wall of the left atrium as witnessed by the atrial contact currents and the damped pressure tracing As withdrawal begins the P_T elevations subside the pulse wave reappears and it is apparent from the morphology of the P waves in the electrogram that the catheter is passing from left to right through the middle of the left atrial chamber The electrode then passes through a small secundum type of defect fairly high in the interatrial septum producing a characteristic flip on the isoelectric line and ends up lying in mid right atrium It is possible from the nature of the P waves in the electrogram to follow its course throughout since having started off low in mid cavity it rises in the left atrium to cross the septum and since withdrawal is from the groin returns to a low mid atrial position again once back in the right heart Although the onset time of the intrinsicoid deflections accurately reflects its position in the heart it should be noted that it does so only as regards the distance between the tip of the catheter and the sinoatrial node At no stage in its route would this help to determine whether the tip was in the right or the left atrium

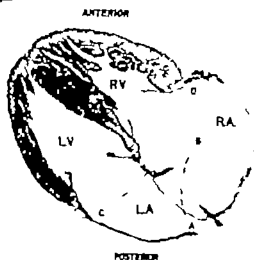


Fig 7 A transverse section of the heart to show the plane of the septa and to demonstrate that the left atrium lies largely behind the right atrium and not alongside it The routes taken by the tip of the catheter in Figs 8 and 9 are indicated by the broken lines

These electrocardiographic observations

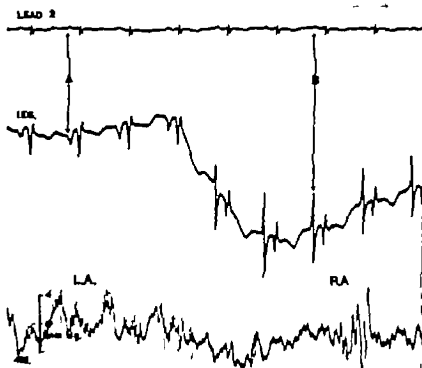


Fig. 8. A withdrawal tracing from a right upper pulmonary vein through a long ovoid secundum defect. In the section illustrated the tip of the catheter started at position A in Fig. 7 high in the left atrium where the P waves are wholly negative. In this position despite the fact that it lies on the left side of the septum the intrinsicoid deflections are early because of the close proximity of the electrode to the sinoatrial node. Once it is through the defect they become later as it recedes to position B in mid cavity of the right atrium.

are in keeping with the anatomy of the heart as it lies *in situ* and much confusion in this as in other spheres stems from failure to appreciate the obliquity of the septa that is when viewed from the front as on an X ray screen the left atrium lies largely *behind* and above the right atrium and not alongside it.[11] The true relationship of the atrial chambers to each other is demonstrated in Fig. 7 from which it is obvious that in many situations an electrode may be nearer to the sinoatrial node in the left atrium than in the right.

This is illustrated in the next two figures withdrawal tracings made as an electrode catheter passed from the left to the right atrium through a long ovoid secundum type of atrial septal defect which had little lower margin and reached down almost to the mouth of the inferior vena cava. The routes taken by the tip of the catheter have been indicated in Fig. 7 one from *A* to *B* the other from *C* to *D*.

In the first it started off in a right superior pulmonary vein and Fig. 8 is the tracing made during its passage from the right upper pole of the left atrium to the middle of the right atrium. The wholly negative P waves confirm that initially the electrode is high in the left atrium and because of its close proximity to the sinoatrial node the intrinsicoid deflections are early despite the fact that it lies on the left side of the septum. As withdrawal proceeds the tip of the catheter flips over the edge of the defect and ends in mid cavity of the right atrium where the intrinsicoid deflections of the now biphasic P waves are somewhat later in onset since in this position the electrode is farther away from the pacemaker.

In Fig. 9 the catheter was withdrawn from a left lower pulmonary vein across the lower edge of the defect into the lower part of the right atrium. The P wave deflections as would be expected are mainly

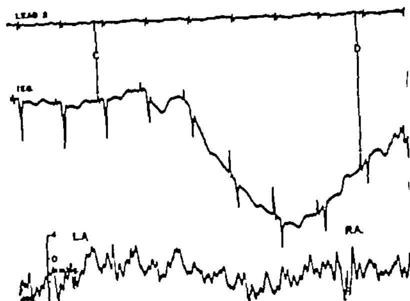


Fig 9 In this record from the same patient as Fig 8 withdrawal was from a left lower pulmonary vein As the defect had little lower rim the electrode remained low throughout its course from *C* to *D* in Fig 7 This reflected in the mainly positive P waves and it should be noted that low in the atria and far from the pacemaker the intrinsicoid deflections are late on both sides of the septum

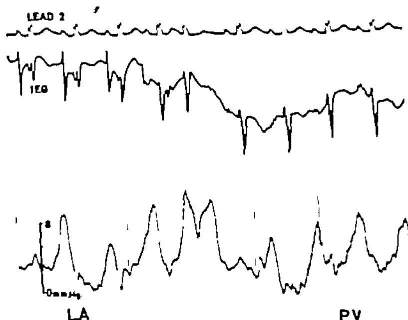


Fig *10* A record made as a catheter was advanced from the left atrium into left upper pulmonary vein The striking change in the morphology of the electrogram shows where the tip has left the heart and marks the insertion of the vessel The early intrinsicoid deflections of the intracardiac P waves however merely indicate that the electrode is fairly high in the atrium and give no indication into which atrium the vessel is inserted

positive and their intrinsicoid deflections are all late falling on the descending limb of the standard lead P waves in the right as well as in the left atrium

These variations again reflect merely the distance between the electrode and the site of atrial activation and are not in any way specific for either chamber It may well be that in practice late P waves will be seen more often in the left atrium than in the right but as will be obvious from these illustrations the timing of their intrinsicoid deflections is completely unreliable as a diagnostic sign It has been said for example that this might help in determining whether a pulmonary vein has an anomalous insertion Fig 10 demonstrates the possible pitfalls associated with the use of such a method for while this tracing was being recorded an electrode catheter was advanced from the left atrium into an upper left pulmonary vein A striking change in the morphology of the electrogram leaves no doubt about where the catheter has left the heart Inside the left atrium there are large P waves and their form indicates that the electrode is fairly high in this chamber An atrial ectopic beat and the characteristic movement of the base line of the electrogram mark the origin of the vessel as the tip of the catheter has flipped over the edge of the atrial wall into the pulmonary vein where the P waves are small and the QRS complexes are the main deflections The intrinsicoid deflections of the intracardiac P waves are early clearly bisect the ascending limb of the P waves in Lead II and give no indication into which atrium the vessel is inserted

Clearly then in normal sinus rhythm the wave of atrial excitation spreads from the sinoatrial node outward and downward through the whole atrial muscle as if there were but one chamber and it is only possible to be certain where an individual complex has been recorded when it is studied in detail along with other information obtained during cardiac catheterization Since the introduction of platinum electrodes the versatility of cardiac catheters has been greatly increased and it seems likely that intracardiac electrography will be used more widely in the future than it has been in the past[1] Already a technique of proved value it is important to realize its limitations and although an electrode at the tip of the catheter is of the greatest possible value during diagnostic investigations it will not by itself distinguish between the right and left atria

Summary

A study has been made of the intracardiac electrograms recorded routinely during 500 consecutive cardiac catheterizations Records from both the right and the left heart were available for comparison in more than 100 cases These have shown that it is not possible to distinguish between complexes recorded in the right and left atria either by studying their morphology or by comparing the time of onset of their intrinsicoid P wave deflections with the P waves in a simultaneously recorded standard scalar lead The intrinsicoid deflections when so measured merely reflect the distance between the electrode at the tip of the catheter and the sinoatrial node

I would like to thank Professor Robert Walmsley for permission to use one of his beautiful sections in Fig 7

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The role of cinefluorography in clinical cardiology: Present and future

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Fluoroscopy, because it permits a study of motion, has always been an essential part of the diagnostic armamentarium of the clinical cardiologist. The usefulness of conventional fluoroscopy, however, is limited by the lack of a permanent record for systematic study. Therefore fluoroscopic interpretations are highly personal. The interpretation must be accepted by others on faith or rejected; rarely can it be debated or modified in light of new clinical developments. Consequently, it is not uncommon for patients to be subjected to the potential hazard of irradiation from repeated fluoroscopic examinations. The inability to obtain a permanent record virtually excludes the application of fluoroscopy to contrast studies of the cardiovascular system. The passage of opaque medium is usually too rapid and the events too fleeting to be followed by the fluoroscopist.

One of the exciting advances of the last decade is the development of a means for intensifying the brightness of the fluoroscopic image. The image may be made bright enough to be photographed for subsequent analysis or to be presented with improved contrast on a television monitor for group viewing in subdued light.

Intensification of the brightness of the fluoroscopic image has been accomplished in a number of different ways. The most widely used method is by means of an x-ray image intensifier tube. Basically, such a tube (Fig. 1) consists of an evacuated glass envelope with an input phosphor (*A*) and an output phosphor (*C*). This output phosphor is backed with a thin layer of aluminum (*B*) to prevent light from returning to the input phosphor. The photons of the x-ray beam (*D*) that pass through the patient are absorbed by the input phosphor, and a light image is produced. A photo cathode layer (*E*), placed in intimate contact with the input phosphor, emits electrons, the point intensity and spatial distribution of which are proportional to the local brightness of the initial image. Thus an electron image is created. The electrons (*F*) are accelerated in their movement down the length of the tube by electrical potentials applied to cylindrical electrodes (*G*) in the tube and impinge on the output phosphor layer, which acts as the anode. A visible image is therefore produced on the output phosphor, duplicating the pattern of that originally present on the input fluorescent layer. Because of the acceleration of the electrons within the tube, the brightness of the image on the output phosphor is many times greater than the original

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image. The brightness is further enhanced by considerably reducing the size of the final image (minification). The image is then brought back to normal perspective by one of several optical systems.

Most image intensifier tubes of this type increase the brightness of the original image 1,000 to 4,500 times. Minification accounts for a gain in brightness of 15 to 50 times. The remaining light intensification is due to electron acceleration.

Such tubes have an input phosphor diameter of 5 to 9 inches. Eleven inch x-ray image intensifier tubes have been made but have proved to be impractical. Larger field size (12 inches) can be accomplished utilizing a lens system (Bouwers) to focus the light image of the fluorescent screen on an image Orthicon tube with a diameter of 4½ inches. The image is transmitted from the Orthicon by closed-circuit television to the viewing monitor. Cinefluorography is available only from the television monitor. Another system with a 12 inch field size utilizes a similar lens system for focusing the image on a 4-inch electronic light intensifier tube. This light image is intensified and focused on the output phosphor and can be scanned by an Orthicon tube for television presentation or photographed as in other systems. Experience with these systems is limited in this country.

Morgan[1] has emphasized that the potential improvement in fluoroscopic vision produced by incorporation of an image intensifier tube diminishes as the viewing distance from the output phosphor increases. The ideal viewing distance of most image tubes is about 20 cm. Unfortunately the optics of a clinically practical image amplifier system places the viewer at a position substantially greater than 20 cm from the output phosphor. Viewing distances in excess of 1 meter usually are required. At such a distance the number of light photons admitted to the eye is substantially reduced, which results in a loss in the potential gain of the intensifier. Therefore image intensifiers when viewed with currently available optics do not produce resolution much better than that of conventional fluoroscopy. The chief advantage of many image intensifiers with an optic viewing system over conventional fluoroscopy is that dark adaptation is unnecessary.

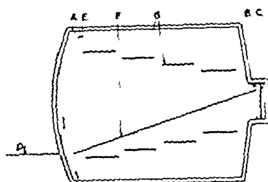


Fig. 1. Diagnostic sketch of an x-ray image-intensifier tube. *A*, Input phosphor. *B*, Thin layer of aluminum. *C*, Output phosphor. *D*, Photons of the x-ray beam. *E*, Photo-cathode layer. *F*, Electron path. *G*, Electrostatic lens.

The gain in brightness and resolution achieved by image amplification may be preserved in a useful form for viewing by photographing directly from the output phosphor or by coupling the intensifier to a television system. With such TV systems contrast may be enhanced and the viewing conditions improved so that resolution may be increased by a factor of two or more. Beam splitters permit the image displayed on the output phosphor to be viewed simultaneously by the TV camera as well as by the photographing camera.

The chief advantage to the cardiologist of image intensification is the ability to obtain a permanent record of the dynamics of the cardiovascular system and the opportunity to see structures that are not visible or are only dimly perceived by conventional fluoroscopy. The recording of the examination may be accomplished by photographing the image from the output phosphor or that presented on a television monitor (kinescopy). There are advantages and disadvantages to both methods. With currently available equipment the resolution is better when filming is done directly from the output phosphor. Filming speeds with kinescopy are limited to 30 frames per second or less but filming directly from the output phosphor allows film speed of 60 frames per second or more. Such filming speeds are necessary to capture rapidly occurring events.

the vascular system. Increased contrast of the image can be introduced electronically, thereby reducing the amount of radiation required when filming is done kineoscopically. It is our opinion that the advantages of filming directly from the output phosphor are more significant than those gained by kineoscopy.

For clinical work a combination of photographing from the output phosphor with simultaneous viewing from the TV monitor is ideal. The TV signal can be fed to a video recorder, permitting immediate playback of the events recorded on film from the output phosphor. Such video playback may lack detail but is of sufficiently good quality to permit the formation of tentative impressions while one awaits the development of the film obtained from the output phosphor. Such a system is used in our laboratory. We have found it to be particularly useful in evaluating patients who are suspected of having intracardiac tumors. One hesitates to pass a catheter into a chamber which contains such a tumor. With video playback the record of the injection of contrast media proximal to the suspected tumor can be evaluated immediately and repeatedly. If no tumor is present, the remainder of the study can be carried out without awaiting the development of the cine film. Such a system is also helpful in confirming immediately the presence or absence of small shunts, the completeness of coronary arterial visualization, etc.

Cinefluorography is useful not only for contrast visualization studies but also in the routine evaluation of patients. The increased brightness permits recognition of more subtle differences of gray due to differences in tissue density. The difference in density between cardiac muscle and small deposits of fat can be readily appreciated. Approximately 95 per cent of adults have a moderately thick deposit of fat lying beneath a part of the visceral layer of the pericardium. In approximately 75 per cent of adults this layer of fat is generous around the apex. Since fat has a density lower than that of body fluids and muscle, it is more radiolucent. It cannot be recognized, however, on routine roentgenograms of the heart and thorax because of the cardiac motion. Nor can it be recognized adequately during conventional fluoroscopy because of the relatively poor resolution that is inherent at the low light levels of conventional fluoroscopy. With the improved resolution of the image amplifier, demonstration of the presence of even a few millimeters of epicardial fat is possible.

Jorgens has emphasized the use of epicardial fat in differentiating a pericardial effusion from cardiomegaly. In the absence of pericardial effusion the motion of the pericardium closely reflects cardiac contractions. The epicardial fat and the pericardial margin move synchronously and with equal amplitude. In the presence of pericardial effusion the epicardial fat is displaced medially by the fluid and becomes more readily recognizable. Being adherent to the epicardium, the fat can be seen to contract vigorously well within the almost motionless and enlarged pericardial silhouette. By sequential cinefluorographic recordings it is possible to follow the course of an effusion.

Deposits of fat are increased in the atrioventricular and interventricular grooves. Therefore, evaluation of specific chamber size is facilitated by image amplification. The increased density due to left atrial enlargement can be readily appreciated. With cinefluorography it is possible to make measurements of chamber size in both systole and diastole. If desired, the electrocardiogram and other physiologic tracings can be recorded directly on the cine film to facilitate timing of the cardiac cycle (Fig. 2). This has been accomplished in our laboratory by means of a small auxiliary oscilloscope (to which is fed the output of an Electronics for Medicine photographic recorder) and a mirror system which directs the light of the auxiliary oscilloscope to the nonemulsion side of the film as it is being exposed to the output phosphor.

Ventricular aneurysms can easily be recognized by cinefluorographic study, and a critical analysis of the expansile characteristics carried out. Serial studies permit value judgments to be made not only of changes in the size of the aneurysm but also in the character of the pulsations. Pericardial fat may be useful in differentiating a ventricular aneurysm from a pericardial cyst or juxtacardiac mass.

The lines of fat are also useful in evaluating calcification that appears to be in or on the heart. As indicated, deposits of fat are increased in the grooves of the heart and the coronary arteries which are frequently calcified traverse these grooves. The main right coronary artery courses in the atrioventricular groove which is best demonstrated in the left anterior oblique projection. The circumflex branch of the left coronary artery passes along the posterior portion of the atrioventricular groove best visualized in the right anterior oblique projection. The anterior descending branch of the left coronary artery passes through the fat deposited in the groove between the right and left ventricles. This groove is also best visualized in the right anterior oblique projection.

Lieber[3] has recently studied the significance of coronary calcification demonstrated by cinefluorography. He concluded: (1) Careful cinefluorography of the heart detects a high number of coronary artery calcifications. (2) Autopsies showed a positive correlation between coronary calcification on cinefluorography and significant coronary atherosclerosis. (3) There is a significantly higher incidence of angina and myocardial infarction in patients in whom coronary calcification is detected cinefluorographically than in patients without such calcification. (4) There appears to be a high correlation between coronary calcification demonstrated cinefluorographically and clinically manifest arteriosclerotic heart disease. It should be noted, however, that cinefluorographic evidence

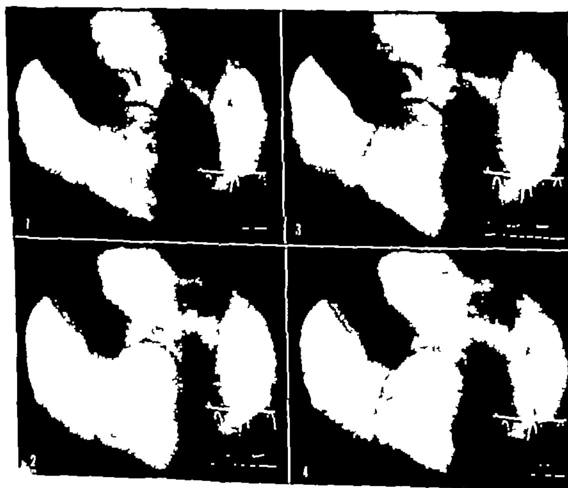


Fig 2. Four successive 35 mm. cineangiogram frames showing injection of contrast media into the root of the aorta. In the lower right hand corner of each frame is superimposed the ECG and the left ventricular pressure.

of coronary calcification by itself is unreliable in predicting the presence of symptomatic arteriosclerotic heart disease

Calcification in the aortic and mitral valves can in our experience be recognized more readily by cinefluorographic study than by conventional fluoroscopy or x-ray techniques Such intracardiac calcification must be differentiated from calcification of coronary arteries the pericardium or rarely mural thrombi Such differentiation is possible by carefully positioning the patient and considering the type of movement and the configuration of the calcium deposits A careful study of the movement of valvular calcification can give some idea as to the mobility of valve cusps It can alert the surgeon as to the possible need for total valve replacement

The diagnostic significance of increased pulsation of the aorta due to aortic insufficiency is well recognized Equally helpful is a study of the pulsations of the secondary branches of the pulmonary arteries When these pulsations are vigorous an atrial septal defect must be considered Whalen[4] in this laboratory analyzed the cinefluorograms (30 frames per second) of 60 patients with various forms of heart disease and of 80 patients without overt heart disease for pulsations of the secondary branches of the right lower pulmonary artery These secondary branches on the right pulsated vigorously in 12 of 13 patients with atrial septal defects The exceptional patient had segmental stenosis of the right pulmonary artery the left pulmonary artery was studied in this patient and was observed to pulsate vigorously All of these patients had normal or slightly elevated pulmonary arterial pressures increased pulmonary flow and increased systolic input into the pulmonary artery Unexpectedly vigorous pulsations persisted in the secondary branches in 4 of 5 patients studied several weeks after correction of their atrial septal defects Pulsations were observed in only 1 of 5 patients with a patent ductus arteriosus and increased pulmonary flow None of 8 patients with ventricular septal defects had secondary pulmonary arteries that pulsated vigorously One of 14 patients with rheumatic heart disease with an elevated pulmonary arterial pressure had vigorous pulmonary arterial pulsations One other patient with severe mitral insufficiency was thought to have such pulsations Closer study revealed that the systolic pulsations in this patient were in a pulmonary vein rather than in a pulmonary artery In only 14 (8 diabetics) of 80 patients without heart disease were significant pulsations observed

In order to assess the relative importance of flow versus pressure in producing such pulsations of the secondary pulmonary arteries cinefluorographic studies were carried out in 6 dogs When a balloon tipped catheter was inflated so as to occlude flow to one pulmonary artery the systolic input into the other pulmonary artery was essentially doubled with no change in pressure The unoccluded pulmonary artery pulsated vigorously After the balloon had been released injection of hypertonic saline into the pulmonary artery produced a marked pulmonary hypertension There was no increase in pulmonary arterial pulsations

It was concluded that accentuated pulsations of the secondary branches of the pulmonary artery were independent of pulmonary arterial pressure and arterial resistance and are for the most part a function of the systolic input into the pulmonary artery There is no increase in pulsations in patients with patent ductus arteriosus because the increased flow is distributed between systole and diastole Ventricular septal defects will pulsate if the shunt is large enough The presence of pulsations in the case of corrected atrial septal defects and diabetes suggests that alterations in the elasticity of the vessel walls may be important in producing pulsations

As has been indicated cinefluorography is ideally suited for angiocardiography Selective cineangiocardiograms supplement other methods currently used in cardiac catheter laboratories for demonstrating intracardiac and extracardiac shunts Relatively small shunts can be demonstrated at all levels within the heart and great vessels We have occasionally demonstrated shunts by cine when determinations of oxygen did not suggest a shunt for example a coronary artery to pulmonary artery fistula was demonstrated when oxygen as well as indicator-dilution data

were normal. A cinefluorogram obtained after left ventricular injection can demonstrate or rule out the presence of a shunt at the ventricular level in patients with a large shunt at the atrial level.

In order to assess the role of cinefluorograms, a retrospective study was designed in our cardiovascular laboratory to compare the diagnostic precision of cardiac catheterization techniques (measurements of pressure and oxygen and indicator-dilution studies) with that of selective cinefluorography. A review was made of the records of 25 consecutive patients with suspected congenital heart disease who were studied by both catheter and cinefluorographic techniques and in whom subsequently a complete diagnosis was made by operation. By the rigid criteria established for this study, which excluded the use of the history, physical findings, or electrocardiogram and x-ray interpretations, the correct and complete diagnosis could be made solely on the basis of catheter data in only 17 of the patients and solely by cinefluorographic techniques in only 19 patients. When the data obtained by both catheter and cinefluorographic studies were combined, a correct and *complete* diagnosis was made in 24 of the 25 patients.

Selective opacification and cinefluorography is admirably suited for studying valvular heart disease, especially insufficiency. A 1+ to 4+ grading can be made which correlates well with the findings at operation. Whether the insufficiency is localized or generalized may be determined. Valvular stenosis can be shown not only by the thickening and immobility of the valve but also by the demonstration of a jet of contrast media when the latter is injected proximal to the stenosis or by a jet-like filling defect in the contrast medium that is injected immediately distal to the stenosed valve.

Coronary and extracardiac arteries can be studied by selective injection of contrast medium. Although definition of such vascular structures may be better with larger film serographic techniques, the ability to appreciate the dynamic properties of the circulation and the significance of obstructing lesions or tortuosity may be of more diagnostic usefulness.

Cinefluorography has wide application in studying basic physiologic problems. Mitral valve function has been studied in detail and correlated with changes in pressure. The flow characteristics of the vena cava, the aorta, and the carotid, coronary, and renal arteries have also been studied. Biplane cinefluorographic units show promise of permitting a calculation of instant-to-instant (60 times per second) changes in ventricular volume.

However, when cinefluorography is to be used for physiologic studies, it must be appreciated that in most commercially available cinefluorographic units no attempt has been made to prevent the introduction of distortion of the image. All radiographic methods with short tube-to-film distances introduce magnification or symmetrical enlargement of the image. Image intensification systems also may introduce distortion (asymmetrical enlargement). Distortion cannot be readily appreciated. If present, it will introduce significant errors in measurements of vascular structures. For example, the diameter of a vessel may be changed simply by viewing it in a different area of the visual field. Barry,[4] in our laboratory, has developed a method for separating magnification of the image from distortion and quantitating the magnitude of the distortion. With careful selection of the amplifying tubes and control of the voltage to the electrostatic lens, it would appear that distortion can be minimized.

Cinefluorography permits the clinician and investigator to study motion. The major disadvantage of cine is the poorer resolving power as compared to conventional large film techniques. The study of single frames projected to life size accentuates the poor definition and grain structure. However, a questionable finding on a single frame may be readily checked on others when up to 60 frames per second are obtained.[4] Rapid serial projection permits integration of single images and thus recognition of structures that would otherwise not be appreciated on single frame visualization. Another disadvantage is the field size. The diameter of the basic image tubes currently available varies from 5 to 9 inches. Systems with 12 inch fields are available as previously described. Their usefulness remains to be seen.

Improvements are occurring rapidly in the field It would appear that definition and resolution will be improved so as to approach the quality of large film techniques When fine detail is the ultimate objective and the recording of motion is of less importance large film techniques are satisfactory However when the analysis of fleeting events occurring within the heart and great vessels is desirable then cine techniques afford otherwise unattainable diagnostic dividends

New advances are constantly being made in cinefluorography Biplane cinefluorographic units are being improved The advantages of such units have been extensively evaluated by Abrams [7] The problems of fogging of the film due to scatter will be obviated with improved collimation and grids Stereoscopic techniques are being developed and evaluated Studies in our laboratory indicate that changes in the TV signal may be utilized as a means of quantitating instant to instant changes in density Such a technique should permit one to more accurately and easily analyze valve motion quantitate the regurgitation or shunting of contrast media estimate chamber volume etc Resolution and detail are constantly being improved both for filming the output phosphor and the TV monitor With improved resolution on the TV monitor it should be possible to take larger films (100 sq mm) with improved detail due to longer exposure time off the TV monitor simultaneously with photography at 60 frames per second from the output phosphor By such a technique it will be possible to obtain at the same time the advantages of improved detail inherent in larger filming techniques as well as the opportunity to study the dynamic characteristics of the cardiovascular system

Cinefluorography has been developed to the point at which it is clinically useful It is no longer a research or laboratory tool Using one of several systems the cardiologist is able to study intelligently the dynamics of the cardiovascular system of his patient The systems have not been developed to the point at which maximum or even satisfactory performance can be expected by those who are not prepared to work at the quality of the output of the individual unit Obtaining high quality films good TV presentation and video playback requires considerable time patience and experience The cardiologist will benefit however by making such facilities available for his use

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Observations in patients with implanted pacemaker

III. Frequency of ventricular tachycardia as cause of Adams-Stokes attacks and rate of pacing required for its prevention

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Syncopal attacks caused by tachycardia are clinically indistinguishable from those due to ventricular asystole or extreme bradycardia. Hence, in the first half of this century, when electrocardiographic records taken during syncopal seizures were not readily available, the concept of ventricular standstill as the cause of syncope dominated clinical thinking. Reports on ventricular tachycardia observed during Adams-Stokes seizures[1-3] were dismissed as isolated instances. In 1927, Wenckebach and Winterberg[4] stated that such arrhythmias, even when they occurred in the presence of A-V block, ought to be strictly separated from genuine attacks caused by real cardiac stand-till. In 1941, Parkinson and associates[5] reported that ventricular tachycardia was the cause of Adams-Stokes seizures in 45 per cent of their cases. In 1948, Schnur[6] stressed that ventricular asystole was still widely believed to be the sole mechanism underlying Adams-Stokes attacks, and as late as 1952, Robertson and Mathews complained that ventricular fibrillation was not generally recognized as a cause of syncopal seizures in the presence of A-V block. In the last decade, study of the mechanism underlying Adams-Stokes seizures received a new impulse from the introduction of new methods of treatment. Moreover, extensive employment of oscilloscope monitors facilitated recognition of the mechanism responsible for syncopal seizures in instances of heart block.

It is the purpose of this communication to emphasize the great frequency of ventricular tachycardia as a cause of Adams-Stokes syndrome, to point out success and failure in the application of available therapeutic means for the prevention of such attacks, and to stimulate discussion on the most suitable rate of electrical pacing for achieving that goal.

Observation on mechanism underlying Adams-Stokes seizures

During the past 25 months, 38 patients suffering from Adams-Stokes syndrome were treated in the Maimonides Hospital with implanted pacemaker. In 28 instances it was possible to determine the nature of the syncopal seizures. Ventricular tachycardia during attacks or a clear prefibrillatory state between attacks was observed in 19 patients, that is, 68 per cent. These figures do not necessarily reflect the actual frequency of ventricular tachycardia, since it is known that in the same patient ventricular asystole may be observed in one seizure and ventricular tachycardia in another.[7,8]

Treatment for prevention of ventricular tachycardia

Knowledge of the great frequency of ventricular tachycardia as a cause of

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Adams-Stokes seizures is bound to influence opinion in regard to prognosis and to underline the urgency of therapeutic action.

1. Use of drugs. Sympathomimetic drugs which are beneficial in patients with asystole are contraindicated when ventricular tachycardia is the mechanism of syncope.[15] Even the short-term use of epinephrine or isoproterenol which was recently again advocated for the prevention of tachycardia[1] is fraught with danger and had better be avoided. The use of digitalis, quinidine, procaine amide, and potassium chloride, designed to depress ventricular excitability, is contraindicated in patients with A-V block who have a disposition to develop ventricular tachycardia.[1, 9, 15]

2. Use of electrical pacemakers. Electrical stimulation of the ventricle is at present the only means for long-term prevention of ventricular tachycardia in cases of heart block.[1] It is assumed that the low rate of heart block predisposes to ventricular tachycardia. Artificial pacemaking is effective by augmenting the basic ventricular rate. The mechanism of this beneficial action is unknown. Zoll[19] suggests that augmentation above the basic ventricular rate increases cardiac output and coronary blood flow and may allow less time for multiple irritable foci to disrupt the ventricular rhythm. The rate of the pacing required to bring about a beneficial effect is still an unsettled question. It appears that in the first attempts at setting a fixed rate of pacing by implanted pacemakers the prevention of ventricular asystole was the primary goal. This could be readily attained by assuring constant ventricular stimulation at a rate of 40 or even 30 per minute. Chardack and associates,[16] who pioneered in the use of transistorized implantable pacemakers, stated in 1960 that a rate of 40 to 50 impulses per minute should be satisfactory. They did not mention the possibility that ventricular tachycardia might be one of the mechanisms requiring treatment. In a later publication[17] (1961) Chardack pointed out that rates in excess of 60 (in adults) are contraindicated. One of the reasons for the wish to keep the artificially enforced rate of ventricular action low was that the use of subnormal rates certainly favors early resumption of idioventricular activity should sudden failure of the artificial pacemaker occur. This concern was not shared by others[4, 19, 15] who empirically chose a fixed pacing rate which ranged from 70 to 80 per minute.

Successes and failures of electrical pacing

In the Maimonides Hospital the General Electric-Kantrowitz implantable pacemaker was employed. It has an inherent rate of stimulus formation of about 60 per minute. The rate can be doubled when there is need by the use of an externally applied induction coil. Among 19 patients who had heart block associated with ventricular tachycardia, a pacing rate of 60 per minute was effective in preventing seizures of syncope in 15 (about 80 per cent); the observation time ranged from 6 weeks to 25 months. Relapses of ventricular tachycardias after implantation was observed in 4 patients, ending fatally in 2.

Case 29. A 68-year-old man developed, on the day of operation, runs of ventricular tachycardia which did not recur after the rate of pacing was increased from 60 to 80 per minute. The length of the observation period after implantation has been 7 months.

Case 27. A 73-year-old woman developed, after implantation, multiple premature ventricular beats which promptly disappeared after the rate of pacing had been raised to 80 per minute. There was no recurrence during an observation period of 9 months.

Case 27. A 6 -year-old man was perfectly well on the first 8 days after implantation and was ready to be discharged. On the morning of the ninth postoperative day he was found in coma. An electrocardiogram (Fig. 1) showed that the pacemaker functioned flawlessly at a rate of 58 per minute. While the tracing was being taken, fatal ventricular fibrillation developed. Postmortem examination revealed no cause of death.

Case 34. A 73-year-old woman developed attacks of ventricular fibrillation during and immediately after implantation. Although the rate of pacing was gradually raised to 95 per minute, seizures recurred. The patient died in an attack of ventricular fibrillation on the evening of the day of operation.

Few reports were found in the literature on the occurrence of ventricular tachycardia after implantation of a pacemaker. Portal and associates[4] observed fatal fibrillation in 2 cases 7 and 2 days, respectively, after implantation. No mention of the

rate of pacing was made. Elmqvist and associates[16] reported also on the postoperative occurrence of ventricular fibrillation. In one case (No. 13) fatal fibrillation occurred on the eighth day after implantation. In another case (No. 9) the arrhythmia was observed on the fifth postoperative day. This patient survived. Electrocardiograms published by the authors show a low rate of pacing (about 30 to 40 per minute). Chardack and associates[17] reported on a fatal attack of Adams-Stokes which occurred 8 months after implantation. The terminal seizure was preceded for a period of weeks by spells of dizziness. At that time investigation showed flawless action of the pacemaker. The authors thought that transient dysfunction of the pacemaker might have been the cause of the fatal attack. They did not discuss the possibility of ventricular fibrillation being the underlying mechanism.

Discussion

Our studies have shown that ventricular tachycardia is the most frequent mechanism underlying Adams-Stokes attacks. Because of its frequent incidence and grave

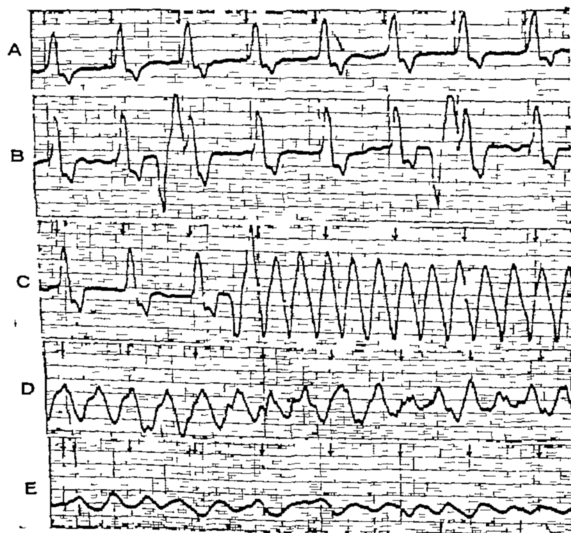


Fig. 1. Case 28. A, *B* and *C* form a continuous tracing. *D* and *E* are part of the same tracing. There is atrial fibrillation. The ventricular action is controlled by the electrical pacemaker which forms stimuli (*see arrows*) at a rate of 38 per minute. In *B* two ventricular premature beats appear. In *C* a similar premature beat is followed by ventricular flutter which in *D* and *E* becomes irregular and turns into fatal ventricular fibrillation. The pacemaker stimuli however are undisturbed.

prognosis prevention of ventricular tachycardia is the chief problem in the treatment of the Adams-Stokes Syndrome. The use of heart-stimulating as well as heart depressant drugs is contraindicated when ventricular tachycardia is the cause of the syncopal seizures. Electrical stimulation of the ventricle is the therapeutic method of choice. It proved to be dramatically effective in the prevention of syncopal seizures in 80 per cent of our cases. Failures were observed in 4 instances. It seems that the period during and immediately after operation is most critical, perhaps because the stress situation lead to a dangerous outpouring of epinephrine which favors the development of tachyarrhythmia in susceptible individuals. Three of our patients developed ventricular arrhythmias on the day of operation. In 2 patients raising the rate of pacing to 80 per minute seemed to abolish further attacks, whereas fatal ventricular fibrillation occurred in one patient even after the rate of stimulation had been increased to 76. In the surviving 2 patients ventricular tachycardia did not recur even when the rate of pacing was later reduced to 60. One patient died of ventricular fibrillation on the ninth postoperative day while the pacemaker functioned perfectly at a rate of 60. There are few reports in the literature of similar observations.

The question may be raised whether electrical stimulation by itself may not be the cause of ventricular premature beats and tachycardias. It is conceivable that pacemaker stimuli when they fall in the vulnerable period of ventricular contraction caused by sinus excitations or of premature ventricular beats may produce ventricular fibrillation provided that they are of sufficient intensity and duration. Such accidents will not occur when the slow idioventricular rhythm is suppressed by the faster acting pacemaker stimuli as happens in most of the cases of heart block. But even when A-V conduction of sinus excitations returns after implantation, accidents are unlikely to occur because the fibrillation threshold as observed in the animal experiment is about 15 times higher than the strength of the impulses delivered by the electrical pacemaker.[3] To be sure the fibrillation threshold may be markedly reduced by ischemia[8] or sympathomimetic effects. Hence the possibility, although remote, that electrical stimulation may exceptionally produce ventricular fibrillation must be borne in mind especially when the pacemaker rhythm is competing with sinus-controlled ventricular action. This possibility could be excluded at least in one of our cases (Case 28) in which registration of the electrocardiogram (Fig. 1) immediately before development of ventricular fibrillation showed that the pacemaker rhythm was in sole control of the ventricles. Moreover, in our Cases 20 and 27 ventricular arrhythmias disappeared promptly after the rate of pacing had been raised to 80 per minute.

Failure of electrical pacing to prevent the recurrence of ventricular tachycardia is bound to raise anew the question of which rate of stimulation is most effective in abolishing the threat of ventricular tachyarrhythmias. The literature gives only a few cursory answers to this question. Schwedel and associates[?] point out that the pacemaker rate is set at 60 per minute when standstill is the mechanism, at 7? per minute or even 80 per minute in fibrillation types. However, as has been stated already, the two mechanisms are often observed in the same patient and observation of the one does not rule out involvement of the other. Zoll and associates[1] state: "The rate of stimulation required to suppress ventricular tachycardia was critical at a particular time in a given patient, although it varied somewhat from time to time in the same patient and varied widely from 45 to 110 beats per minute from patient to patient." Such a wide range can only mean that it is safest to choose the highest possible fixed rate of stimulation. Even the use of a pacemaker with a rate adaptable to needs is not always a safe solution. It helped in our Cases 20 and 27 but could not prevent a fatal outcome in Case 34 in which apparently attacks of fibrillation had occurred unobserved during the night and the first observed attack proved fatal. In the choice of a suitable inherent rate of pacing technical considerations will also play a role. The desire to keep down the size of an implanted pacemaker and to increase

the variability of the batteries will limit the rate of electrical stimulation. The latter is of necessity a compromise between medical requirements and technical possibilities. It will be up to the electrical engineers to solve the technical problem. Under the prevailing circumstances it seems that an inherent pacing rate of 90 per minute which could be increased to as much as 120 per minute when the need arises would go far toward preventing the development of ventricular tachycardia. At the same time it would satisfy the need for a greater cardiac output in the presence of congestive heart failure which so frequently accompanies Adams-Stokes disease, and in patients with insufficient cerebral and renal circulation.

Of course some rare cases may be encountered in which the disposition to ventricular fibrillation is so overwhelming that it could not possibly be changed by the mere speeding up of ventricular contractions.

Summary

Thirty-eight patients with Adams-Stokes syndrome were treated with implanted pacemakers. In 28 the mechanism of syncope could be determined. Ventricular tachycardia was observed in 19, that is, in about 68 per cent.

Because of the great frequency of this arrhythmia and the grave prognosis attached to it, prevention of ventricular tachycardia is the *chief problem in the* treatment of Adams-Stokes syndrome.

The use of sympathomimetic and cardiac depressant drugs is contraindicated. Stimulation of the ventricle by an electrical pacemaker is the only promising method of treatment. Pacing at a rate of 60 per minute was effective in the long-term prevention of ventricular tachycardia in 15 out of 19 patients. In 3 patients ventricular arrhythmias recurred on the day of implantation. Raising the rate of pacing from 60 to 80 per minute prevented further attacks in 2 patients. In the third patient, however, fatal ventricular fibrillation recurred on the day of operation after the rate of pacing had been stepped up to 96 per minute. A fourth patient succumbed to ventricular fibrillation on the ninth postoperative day while function of the implanted pacemaker at a rate of 60 per minute was unimpaired.

It is suggested that implantable pacemakers, in order to yield full benefit, should have an inherent pacing rate of 90 per minute. Provision should be made, if possible, for increasing the rate of the pacemaker so that its function may be adapted to changing needs.

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Changes in bone associated with cyanotic congenital cardiac disease

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Roentgenographic changes in bone are an unusual concomitant of congenital heart disease. Changes in the configuration of the thoracic cage may occur, and rib notching may result from obstructive lesion of the great vessels, particularly coarctation of the aorta. These alterations affect the external contour of the bones. Recently we have observed 6 patients ranging in age from 19 months to 42 years who have shown intrinsic changes in bone associated with cyanotic congenital heart disease. Ascenzi and Marinozzi[1] apparently were the first to recognize thickening of the skull associated with cyanotic congenital cardiac disorders with polycythemia. At autopsy the bone marrow showed hyperplasia and congestion. In their article a cross section of the skull and histologic preparations of bone are reproduced. Mariam and Bosman[11] in a thorough discourse reported on 26 patients from 1 to 39 years of age with cyanotic congenital cardiac disorders. These include 2 with truncus arteriosus, 14 with tetralogy, two with trilogy, and 8 with pentalogy of Fallot. Their studies included roentgenograms of the skull in 18 and of the sternum and spine in 25 patients. Diploic thickening of the skull was present in 3 patients. The spine was not remarkable in most cases; it showed only thinning of the upper and lower margins of the vertebral bodies in 6 instances, and the sternum was involved only once. Microscopic studies showed marrow hyperplasia in all cases. The changes were more pronounced with advancing age. We have found only a mention of this condition in two American publications.[9,12] For this reason we thought that publication of these cases would be worth while.

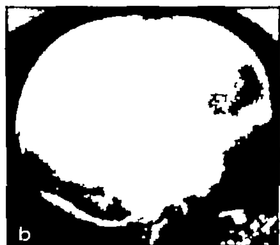
Case reports

Of the 6 cases reported below, the first 3 are from the files of the Charity Hospital in New Orleans and the other 3 from the University of Colorado Medical Center in Denver.†

Case 1. D. W., a 10-year-old white girl, has been cyanotic since birth. The patient had many acute febrile illnesses during the first year of life and also

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†The cooperation of Dr. S. Gilbert Blount, Jr., Chief of the Division of Cardiology, University of Colorado Medical Center, is acknowledged.





Figs. 1a and b. Case 1. Posteroanterior and lateral views of the skull showing thickening of parietal bone with moderate thickening of the rest of the cranial vault.

several episodes of congestive heart failure. At the age of 4, two episodes of severe icterus without additional systemic signs occurred. In February 1957 a diagnosis of hepatitis was made. From that time on the patient had hepatosplenomegaly. Physical examination, electrocardiography, and cardiac catheterization resulted in a diagnosis of transposition of the great vessel with interventricular septal defect. Laboratory examination revealed a hemoglobin level varying from 13 to 23 Gm. per cent. The packed cell volume went as high as 69 per cent. The reticulocyte count was 13.6 on one occasion. Hemoglobin electrophoresis revealed A hemoglobin.

Chest films demonstrate cardiomegaly with increased pulmonary vascularity. Roentgenograms of the skull show moderate thickening of the diploë in the frontal region and considerable thickening in the parietal region (Fig. 1a and b). Roentgenographic study of the distal ends of the long bones reveal widening of the medullary cavities, cortical thinning, and coarsening of the trabecular pattern. The same changes are also noted in the hand and wrist (Fig. 1c). A roentgenogram of the abdomen and pelvis shows hepatosplenomegaly, gallstones, and similar bone changes in the lumbosacral spine, pelvis, and upper portion of the femoral bones (Fig. 1d).

Case 2. A. J., a 7-year-old Negro girl, has been cyanotic since birth. She has been admitted to the hospital several times for acute febrile illnesses and some episodes of failure. Examination revealed signs of heart failure, hepatosplenomegaly, and clubbing of the fingers and toes. Electrocardiography and cardiac catheterization along with the other clinical data indicated transposition of the great vessels with a probable ventricular septal defect. The hemoglobin was 15 Gm. per cent with a packed cell volume of 60 per cent.

Roentgenograms of the skull reveal widening of the diploic space, especially in the frontal region (Fig. 2a). A roentgenogram of the abdomen and pelvis shows moderate enlargement of the liver and spleen with increased radiolucency of the lumbosacral spine and pelvis (Fig. 2b).

Case 3. R. H., a 17-year-old white boy, has been cyanotic from birth. He was never able to lead a normal life because of periodic episodes of shortness of breath, cyanosis, weakness, and chest pain. He has had polycythemia and has required phlebotomy several times. On admission the patient was noted to be cyanotic and there was clubbing and spooning of the fingernail and toenail. Physical examination, electrocardiography, and cardiac catheterization resulted in a diagnosis of tetralogy of Fallot.

Roentgenograms of the skull show thickening of the diploic space to a moderate degree throughout the cranial vault. Increased radiolucency with slight coarsening of the trabecular pattern is noted in the hands and wrist, ends of the long bones, lumbosacral spine, and pelvis.

Case 4. T. L., a 19-year-old white boy, has been cyanotic since birth. He was first seen at age 9 when clinical studies including cardiac catheterization indicated a single ventricle with transposition of the great vessels. He has followed a progressively deteriorating course and during the past year before his most recent admission he has had congestive heart failure intermittently and has experienced increasing difficulty with exertion. He appears to be quite cyanotic at rest. Repeat catheterization confirmed the original findings. Selective angiocardiography demonstrated a single ventricle. The aorta was leftward and anterior in a position usually associated with corrected transposition.

Chest films show increased pulmonary vascularity and a left cardiac contour suggestive of corrected transposition. Sclerotic changes are noted in the ribs. The films of the skull show selective thickening of the orbital plates and the frontal bone. The lateral roentgenogram of the lumbar spine shows

peculiar wedge shaped sclerosis of the anterior portions of the vertebral bodies (Fig 3 *a*) There is mild thickening of the metacarpal cortices and coarsening of the trabecular pattern of the bones of the distal forearms (Fig 3 *b*)

Case 5 W B a 42 year-old white male deaf mute had been cyanotic since childhood Clubbing of the fingers and epistaxis had been prominent features of his illness Secondary polycythemia became a problem at the age of 12 He was treated unsuccessfully with P³² in 1954 Numerous phlebotomies were performed during the last years of his





Fig 1 Case 1 Supine view of abdomen showing large liver and spleen gall tones and increased radiolucency of the bones of the lumbo-sacral spine and pelvis with secondary trabecular pattern



Figs 1c and d Case 1 Expansion of medullary cavity increased radiolucency thinning of cortex in long bones and hand



Fig 1f Case 1 Lateral view of sternum showing deossification of lower portion (arrow)

life. Pulmonary osteoarthropathy was noted roentgenographically in 1954. A duodenal ulcer was diagnosed in March 1960, approximately 1 year *before he died*. Laboratory data revealed a hematocrit of 64 per cent and hemoglobin of 17.3 Gm. The patient died at 4? years of age; the final diagnosis was pulmonary arterial thrombosis due to polycythemia and pulmonary hypertension, ventricular septal defect with reversed shunt (Eisenmenger





Fig. 2. Case 2. *a*, Lateral view of skull showing thickening predominantly in frontal region. *b*, Supine view of abdomen and pelvis showing very slight enlargement of liver and spleen but with increased radiolucency of the lumbosacral spine and pelvis with secondary prominent trabecular pattern in the pelvis.





Fig. 3. Case 4. *a*, Increased opacity of the ribs; increased radiolucency of vertebral bodies with patchy sclerosis especially along anterior margin. *b*, Sclerotic changes in the distal end of the radium and ulna of both forearms. Increased radiolucency in the carpal bones and about the joints of the hand and wrist, with very slight thickening of cortex of the metacarpals and proximal phalanges.

syndrome) bleeding peptic ulcer and gout. No autopsy was performed.

Roentgenogram of the chest box bulking consistent with an interventricular septal defect with pulmonary hypertension. Anteroposterior and lateral views of the right ankle demonstrate a coarsened trabecular pattern and cortical thickening with periosteal reaction between the tibia and fibula in the distal third (Fig. 4a). The roentgenogram of the lumbosacral spine and pelvis demonstrates a somewhat coarsened trabecular pattern with mottled areas of sclerosis (Fig. 4b).

Case 6. S.S., a 19 month-old white male, had been cyanotic since birth. Asymmetry of the skull, prominence of the right anterior chest and clubbing of the digits were prominent clinical features. Laboratory data revealed a rapidly rising hematocrit which had reached 85 per cent just prior to death. Clinical evaluation and angiographic studies had established the presence of cyanotic heart disease with multiple congenital defects. The findings at autopsy included dextrocardia, cor biloculare, truncus arteriosus, and anomalous azygous vein. The stomach and spleen were on the left; otherwise there was complete situs inversus.

The remarkable roentgenographic osseous findings were confined to the skull. There was marked parietal thickening with a striated "hair-on-end" appearance.

Discussion

The bony lesions encountered in these 6 cases can be roughly subdivided into two



Fig. 3c. Case 4. Lateral view of sternum showing sclerotic cortex.





Fig. 4. Case 5. a, Expansion of medullary cavity, thinning of cortex, and increased radiolucency in the distal end of the tibia and fibula as well as the talus; periosteal reaction between the distal ends of the two long bones. b, Radiolucent changes with prominent trabecular pattern interspersed with sclerotic changes in the pelvis and to a lesser extent in the lumbosacral spine.

categories on the basis of their similarity to other lesions with which we are more familiar. The periosteal deposition which thickens the cortex of the mid or distal shafts of long bones is identical to pulmonary osteoarthropathy. This entity is frequently associated with digital clubbing and occasionally with arthralgia with or without effusions in the joints and is encountered in patients with chronic suppurative or neoplastic pulmonary disease. Its occurrence with congenital heart disease has also been described[14] and the neurovascular mechanism which has been



Fig 5 Case 6 This 19 month old infant with severe cyanotic congenital heart disease had a rather considerable degree of sclerosis of the parietal bone with a radiating pattern noted in the lateral view. The anteroposterior view is not reproduced but showed very characteristic hair-on-end appearance similar to that in Fig 1

hypothesized on the basis of the salutary effect of vagectomy[1] is probably the same regardless of the etiology Thus bony abnormalities in patients with congenital heart disease such as those seen in the ankles in Case 5 Fig 4a can probably best be designated pulmonary osteoarthropathy

The bony abnormalities of particular interest encountered in our cases are changes which we generally associate with chronic anemias These abnormalities include *skull*—widening of the diploe thickening of the tables and the hair on end striations *long bones*—endosteal cortical defects widening of the medullary canals loss of diaphyseal tapering loss of trabeculation in some areas and coarsening in other areas *pelvis spine and ribs*—mottled areas of sclerosis and/or alterations in trabecular pattern Individually or as a group these abnormalities of the bones have been described in Cooley s anemia[3] congenital hemolytic anemia[4] sickle cell disease[5,10] polycythemia vera[6] chronic iron deficiency anemia[7] and myeloid ... plasia[12] The hyperplastic ma... may result from constant st... causes endosteal cortical erosion medullary cavities and obliterat... beculae producing the radiol cent

genographic findings The sclerotic changes are the result of the deposition of new bone on existing bone or osseous metaplasia in the marrow spaces Apparently this happens with both hyperplastic marrow as in the calvaria of patients with sickle cell anemia and aplastic marrow as in the fibrous tissue of patients with myeloid metaplasia The exact mechanism is uncertain but clearly the same factors are operative in patients with cyanotic congenital disease—the hypoxemia is a constant stimulus to marrow activity

Consideration should be given to the possibility that infarction plays some role in producing these changes in bone since bone infarction does produce sclerosis and since infarction is likely to occur in the presence of polycythemia Of the anemias sickle cell disease most frequently presents with roentgenographic evidence of bone infarction The patterns of infarction commonly seen in that disease are not reproduced in our cases (calcification in the medullary canal transient periosteal reaction or aseptic necrosis in hard working cancellous areas such as the femoral or humeral heads) On the other hand it is difficult to explain such a pattern of sclerosis as that seen in the vertebral bodies of our Case 4 without envoking some vascular factor Careful histologic analysis of postmortem specimens would be necessary to resolve this issue

Finally it should be noted that periosteal new bone formation identical to pulmonary osteoarthropathy has been described in patients with myeloid metaplasia[12] patients who have the other osseous stigmata of anemia So it is possible that all the changes in bone noted in our patients are a result of the secondary polycythemia and that a neurovascular pulmonary mechanism is not a factor

Summary and conclusions

Cyanotic congenital cardiac disorders ... acc... nied by roentgenographi... t... changes in bone These ... hanges include diploic th... radiolucent and radi... metaphyses of he lo... nd pelvis and t... nds of long ... te that

chronic hypoxemia produced by right to left shunts results in hyperplasia of the bone marrow which in turn leads to polycythemia and the roentgenographic changes in bone described and reproduced herein

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Arrhythmias after cardiac surgery

II Cyanotic tetralogy of Fallot, with comments in regard to ventricular septal defect

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A former communication[1] dealt with arrhythmias which occur after the surgical correction of atrial septal defects. Total correction of tetralogy of Fallot with which the present report deals is a far more stress producing procedure that involves primarily the right ventricle. Therefore a study of arrhythmias which occur during the postoperative period would possibly bring to light quite different aspects of the over all problem of arrhythmias after cardiac surgery. In addition the possible effect of ventriculotomy was studied by also analyzing patients who had undergone correction of uncomplicated ventricular septal defect.

Material and methods

This study is based on 60 consecutive patients with cyanotic tetralogy of Fallot who underwent an open heart operation in an attempt to produce complete correction of their lesions. Two of these patients had undergone two such procedures so that this series covers 62 operations. These operations were performed at Presbyterian Medical Center in San Francisco between Jan 1 1959 and May 1 1963. In addition an analysis was made of the electrocardiograms of 97 patients with uncomplicated ventricular septal defect.

The diagnosis was established by cardiac catheterization and/or biplane angiography in every instance. The patients with so called acyanotic tetralogy of Fallot were not included since the study dealt only with patients who had arterial desaturation at rest or who had been desaturated at one time and subsequently had undergone a palliative procedure such as a Brock or Blalock-Taussig operation. A number of patients also had atrial septal defects or large patent foramen ovale. The surgical technique of repair has been described in detail previously.[2]

A complete electrocardiogram was recorded on every patient prior to operation

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Table I Total number of arrhythmias encountered in patients with tetralogy of Fallot

Arrhythmia	Total number of arrhythmias	Major type in each patient
Supraventricular tachycardia	12	[illegible]
A-V dissociation	10	[illegible]
Nodal rhythm	7	4
Second-degree heart block	3	2
Wandering pacemaker	2	
Frequent premature ventricular beat	2	
Atrial flutter with 2:1 and 3:1 block	2	2
Atrial tachycardia with 2:1 block	1	1
Ventricular flutter	1	1
Frequent premature atrial beat	1	–
	41	23

Table II Arrhythmias and sex distribution

	Males	Females	Total
Total number of patients	36 (63%)	21 (37%)	57 (100%)
Patients with arrhythmias	13 ([illegible]%)	10 (44%)	23 (40%)

and on the day before discharge from the hospital approximately 14 days after the operation. For the first 2 postoperative days there was continuous monitoring of the electrocardiogram and partial electrocardiograms (rhythm strips) were taken daily for 3 days. In most cases additional tracings were recorded. All these studies were reviewed by the senior author.

Pertinent details of extracorporeal circulation were noted; these included the total duration of perfusion, the degree of hypothermia used, and the use of hydrochloric acid.[4] Frequent blood gas and electrolyte studies were also reviewed.

Results

Of the 62 operations analyzed, 5 were not included in this study of arrhythmias for reasons which will be mentioned at the end of this section. Twenty-three of the other 57 patients (40 per cent) developed an arrhythmia. There was a total of 41 arrhythmias which indicates that many patients had more than one type. The incidence of the most persistent or serious arrhythmia in each patient is shown in the right hand column of Table I.

Table III Incidence of arrhythmias in relation to the age of the patients

Age (yr.)	Number of cases	Number with arrhythmias	
0–6	30	14	47
9–17	17	7	41
18–3	10	2	20%

Analysis for sex and age is shown in Tables II and III, respectively. There is a predominance of males over females in the group as a whole which agrees with the findings of other workers.[3] This trend persists in patients with and without arrhythmias. The incidence of arrhythmias in patients 18 years or older is half that found in those under 18 years of age.

Of the various types of arrhythmias encountered, supraventricular tachycardia and atrioventricular (A-V) dissociation were the most common. The latter is defined as having an independent atrial and ventricular rate. The ventricular rate is faster than the atrial rate and the QRS complexes appear to have a normal supra

Table IV Effect of changes in extracorporeal perfusion in patients with and without arrhythmias

	Sinus rhythm	*Arrhythmias*	*Total*
A Average total length of perfusion	1 hr 57 min	2 hr 23 min	2 hr 8 min
B Hypothermia			
35° – 26°	4 (50%)	4 (50%)	8
25° – 20°	21 (57%)	16 (43%)	37
20° – 13°	9 (75%)	3 (25%)	12
	34 (60%)	23 (40%)	57
C Use of HCl during cooling (Edmark technique)			
HCl used	12 (60%)	8 (40%)	20
HCl not used	22 (60%)	15 (40%)	37
	34 (60%)	23 (40%)	57

ventricular configuration Furthermore the normal conduction mechanism is demonstrated by the occasional captured beats This fact and the rapid ventricular rate distinguish A V dissociation from the postsurgical heart block Of the 10 cases of A V dissociation 8 occurred immediately after the operation and 5 of these had reverted to complete sinus rhythm spontaneously 1 to 9 days later One patient died after 2 days because of severe respiratory insufficiency (he was not in complete heart block) and another patient who had undergone her second open heart operation was in partial A V dissociation 5 months later showing sinus rhythm at times The eighth patient still revealed complete A V dissociation having a ventricular rate of 50 to 66 per minute without needing any medication The 2 patients who subsequently developed A V dissociation were examples of digitalis toxicity and will be mentioned later

Supraventricular tachycardias also occurred primarily immediately after operation and these arrhythmias reverted to sinus rhythm within the first 48 hours usually requiring treatment There were 4 patients who developed a supraventricular tachycardia between the fourth and twelfth postoperative day and in at least 3 of these the cause was digitalis

Nodal rhythm second degree heart block and wandering pacemaker were usually present as an interim rhythm when the electrocardiogram was reverting from A V dissociation to sinus rhythm or they were present for only a short period of time after the operation All patients with such arrhythmias had sinus rhythm before they were discharged from the hospital

Atrial flutter with 2 1 and 3 1 block occurred in 2 patients A 5 year old boy had a stormy postoperative course after complete repair of his lesion which included complete atresia of the outflow of the right ventricle He was improving and in sinus rhythm when he developed atrial flutter with block on the twelfth day The digoxin was discontinued and sinus rhythm was restored 2 days later The other case of atrial flutter with block occurred in a 13 year old girl on the fourteenth day She was in severe right heart failure due to pulmonary hypertension (she had previously undergone a Blalock anastomosis) with subsequent pulmonary insufficiency There was also a small residual ventricular septal defect This was treated with quinidine and sinus rhythm was present 2 days later The digoxin was not stopped

Atrial tachycardia with 2 1 block occurred in a 31 year old woman 18 days after operation This was the only case of renal failure in the entire series Unfortunately digitalis was continued during the anuric state and the severe hypokalemia which developed as a result of diuresis produced fatal digitalis intoxication

The one instance of ventricular flutter

occurred in a 4 year old girl. She also had a stormy postoperative course after complete correction of her lesion, which included atresia of the pulmonary valve. Her electrocardiogram revealed supraventricular tachycardia for most of the first 2 days, and this finally became so rapid that hypotension ensued. Various drugs were used and these eventually produced ventricular flutter. This was changed to sinus rhythm after cardiac massage and electrical defibrillation. The patient made a slow but complete recovery.

Table IV compares the two groups of patients in respect to length of perfusion, the degree of hypothermia used, and the use of hydrochloric acid during the cooling stage of perfusion. It is clear that none of these factors influenced the occurrence of arrhythmias.

Five of the 62 operations were not included in the tables for the following reasons. There was one case of complete heart block surgically induced. This was one of the last patients in whom potassium arrest was used. He is quite well 4½ years after his operation, but he requires Isuprel occasionally. One patient, a 7 year-old girl with very severe cyanosis, had complete A-V dissociation prior to her operation. Records dating back for 5 years showed this rhythm with normal QRS complexes but a ventricular rate of between 50 and 65 per minute. Ten days after operation, regular sinus rhythm appeared for the first time and is present 6 months later. This most unusual case is not fully understood, but it may be due to improved myocardial oxygenation and conduction system metabolism. Three other patients were not included in the study because they died in the operating room.

Discussion

The final outcome of a technically successful operation for the correction of a cardiac defect may be jeopardized by the occurrence of an arrhythmia during the recovery period. Our observations have helped us to determine the etiology of many of these arrhythmias, and this in turn has led to a lower incidence of arrhythmias and also to improved management when they do occur.

When the clinical course of patients with arrhythmias in the tetralogy group is reviewed, it becomes evident that the precipitating factors fall into three main categories: (1) acidosis and/or anoxia, (2) drugs (digitalis in this case), and (3) operative trauma. Acidosis, whether metabolic or respiratory, is poorly tolerated by

Table V. Arrhythmias in patients after closure of ventricular septal defect

	Without pulmonary hypertension	With pulmonary hypertension	Total
Total number of patients	60	37	9
Patients with arrhythmias	5 (9%)	15 (41%)	70 (20%)

Table VI. Total number of arrhythmias encountered in patients with ventricular septal defect

Arrhythmia	Total number of arrhythmias	Major type in each patient
A-V dissociation	9	8
Nodal rhythm	7	5
Supraventricular tachycardia	5	4
Atrial tachycardia with 2:1 block	2	2
Ventricular tachycardia	1	1
	24	20

patients whose cardiac reserve is limited. At least 6 of the 23 patients had arrhythmias which were due to this cause, and they usually showed a supraventricular tachycardia of 150 to 190 per minute during the early postoperative period. Their arterial pH ranged from 7.20 to 7.25, and the arterial pCO_2 was between 56 and 71 mm. Hg. One patient, however, was able to compensate quite well for her respiratory acidosis, having an arterial pH of 7.47 and arterial pCO_2 of 75 mm. Hg. Before we became aware of the etiology, we digitalized these patients, and frequently there was no response. More recently, this situation has been solved by either giving sodium bicarbonate and/or using assisted ventilation, depending upon the result of blood gas analysis. At times a low arterial pO_2 has been found,[6] and rectification of this has also resulted in elimination of the arrhythmia.

The second cause of arrhythmias in our series was digitalis intoxication. At least 8 patients fell into this category. These arrhythmias usually occurred after the fourth day and were managed without difficulty by the withholding of digoxin. One patient was treated successfully with potassium. As previously mentioned, there was one fatality in this category. There is ample evidence that cardiopulmonary bypass enhances the sensitivity of the patient to digoxin.[7] The amount of digoxin now used is less, and it is rarely given before the fourth postoperative day.

The third cause of arrhythmias can be termed "operative trauma." A small number of patients revealed nodal rhythm or A-V dissociation soon or immediately after operation but did not have a fast rate and were comfortable. This is the same situation as was found in our previous study[1] in regard to atrial septal defects. When the operative report is reviewed, it becomes evident that these patients had undergone an additional atriotomy for closure of a large patent foramen ovale or separate atrial septal defect. There is one patient who has complete A-V dissociation but does not require any medication and must be considered as belonging to this group of 5 patients.

In 4 of the patients it was not possible to decide for certain what caused the arrhythmia, although a mild degree of acidosis was probably present.

The absolute incidence of arrhythmias in patients who have undergone complete correction of tetralogy of Fallot appears to be the same as that in those who have undergone closure of their atrial septal defect. In the latter series, we showed that the incidence and severity of the arrhythmias was in direct proportion to the age of the patient. It was extremely rare that a patient under 18 years of age had an arrhythmia which required management. The exact opposite was found in the study of tetralogy. This may be due to the more severe hemodynamic and respiratory changes which occur after this type of operation. On the whole, the younger patients were the ones with a more severe degree of pulmonic stenosis. That the right ventriculotomy per se is not responsible for arrhythmias is well shown in Table V. In a review of the operative repair of ventricular septal defects without pulmonic stenosis, only 20 out of 97 patients had arrhythmias, and none occurred in patients over 18 years of age. Table VI shows that the types of arrhythmias encountered are very similar to those in patients with tetralogy of Fallot. The outstanding point, though, is that most of the arrhythmias occurred in patients with pulmonary hypertension, and these are the patients who are likely to develop acidosis and anoxia.

Our findings indicate that the occurrence of an arrhythmia early during the postoperative period may be the first sign of trouble. The immediate concern should be the general condition of the patient, and the use of digitalis, quinidine, or other antiarrhythmic drugs is not indicated in most instances. The mortality after operation for tetralogy of Fallot has fallen from 33 per cent in 19?9 to less than 10 per cent at the present time. Improvement in surgical and perfusion techniques is in large part responsible for this, but the improved understanding of the etiology and management of arrhythmias has also contributed to the reduced mortality rate.

Summary and conclusions

In 60 consecutive patients who underwent open-heart operation for complete

correction of cyanotic tetralogy of Fallot the frequency of the various postoperative arrhythmias has been studied and correlated with various predisposing and precipitating factors

The total incidence of arrhythmias in this series is 40 per cent The etiology of these arrhythmias falls into three categories (1) acidosis and/or anoxia (2) digitalis toxicity and (3) operative trauma

In the event of a postoperative arrhythmia the cause should first be searched for and rectified This approach has contributed to the reduced mortality rate and decreased morbidity

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The second heart sound in biventricular failure due to African cardiomyopathy

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It has been shown[1] that in chronic constrictive pericarditis the aortic second sound (A_2) can be seen on the phonocardiogram to move toward the relevant R wave of the electrocardiogram immediately after inspiration begins. The result is an early exaggeration of the splitting of the second sound that normally occurs on inspiration. It seemed of interest, therefore, to observe the behavior with respiration of the second sound in African cardiomyopathy, which is marked by biventricular dilatation and failure in the absence of valvular abnormalities or other relevant complications,[2] and to compare it in cases of acute tuberculous pericarditis.

Material and methods

Nine patients who were suffering from biventricular failure due to typical African cardiomyopathy were studied, and 3 patients with acute tuberculous pericarditis were studied for comparative purposes. None of the patients had conduction defects. Phonocardiograms were recorded with a Sanborn Twin Beam phonocardiograph; one channel recorded heart sounds from the pulmonary area, and the other recorded Lead II of the electrocardiogram or the carotid impulse. A_2 was identified by its relation to the carotid pulse or by its intensity relative to the pulmonary second sound (P_2) at the apex. Inspiration was signaled on the record by the recorder.

The intervals between the peak of the R wave and A_2 (R-A_2), between the R wave and P_2 (R-P_2), and between A_2 and P_2 (A_2-P_2) were measured in each case; the measurements were taken from the last cardiac cycle in expiration and the first cycle of inspiration which followed over at least two consecutive respiratory cycles. The point in the vibration complex which corresponded to a sound that was taken for purposes of measurement was the point of maximum deflection.

Results

The findings in the cases of African cardiomyopathy are given in Table 1. The figures represent the means of values obtained for the number of respiratory cycles. It was found that when two cardiac cycles fell within the period of inspiration, the values obtained in the second of these were identical to those in the first.

In 7 cases, therefore, R-A_2 stayed unchanged, and in 2 it was prolonged by an insignificant amount early in inspiration. In 4 cases R-P_2 stayed unchanged, and in 5 it changed insignificantly—in 4 by lengthening and in 1 by shortening early in inspiration. A_2-P_2 therefore remained fixed in 3 cases, but in early inspiration

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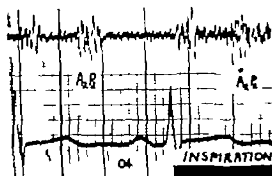


Fig 1 The top tracing is the phonocardiogram the bottom tracing is Lead II taken from a patient with African cardiomyopathy Show fixity of the R A₂ interval in relation to respiration

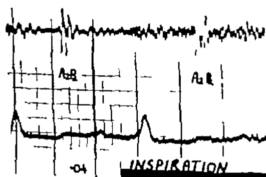


Fig 2 Same as Fig 1 in another patient with African cardiomyopathy

it lengthened in 4 and shortened in 2 cases the greatest change being a prolongation of 0 01 second Examples are given in Figs 1 and 2

In the 3 cases of acute tuberculous pericarditis each examined over three consecutive respiratory cycles the mean R A_2 intervals were 28 35 and 31 hundredths of a second in expiration and 26 33 and 30 hundredths of a second in inspiration An example is given in Fig 3

Discussion

The effect on the second heart sound of heart failure uncomplicated by valvular or congenital heart disease has been little studied Perloff and Harvey[2] demonstrated that right ventricular failure caused the pulmonary second sound to become fixed in respiration in its relation to the ventricular complex of the electrocardiogram in right and left bundle branch block and in mitral incompetence It is not surprising that fixity in respiration of A_2 should also result from fixity of left ventricular output by failure as appears from the present results It is possible that this behavior



Fig 3 Tracings taken from a patient with tuberculous pericarditis In the first cycle to occur within the inspiratory phase the R A interval decreases

Table 1 Findings in patients with African cardiomyopathy (mean figures in hundredths of a second)

Case	Number of respiratory cycles	R 1		R I		1–I	
		Expiration	*Inspiration*	*Expiration*	*Inspiration*	*Expiration*	*Inspiration*
1	3	28	28	34 7	34	6 7	6
2	2	38	38	43	43	5	5
3	4	36 25	36 75	43	43	6 75	6 25
4	5	37	41	37 5	37 9	5 5	5 9
5	2	29	29	32	32	3	3
6	2	25	25	29 5	30	4 5	5
7	2	30	30	32	33	2	3
8	2	31 5	32	35 5	36 25	4	4 25
9	3	29	29	34 3	34 3	5 3	5 3

of A will provide a further means of distinguishing cardiac tamponade from cardiac dilatation which differentiation has recently been discussed by Burch and Phillips[4] This would be particularly valuable if the form of tamponade found in tuberculous pericarditis had effects on the second sounds similar to those of constrictive pericarditis since tuberculous pericarditis is the main condition that makes diagnosis difficult in a population which is prone both to it and to African cardiomyopathy There is evidence from the 3 cases studied that the effects are similar Moreover there is presumptive evidence from the study of the hemodynamic effects of experimental acute tamponade by Golinko and associates[5] whose findings were similar to those recorded in constrictive pericarditis[1]

Summary

The aortic and pulmonary second sounds were timed after the R wave of the electrocardiogram in 9 patients with biventricular heart failure due to African cardiomyopathy The aortic sound remained fixed in its time relation during the different phases of respiration whereas the pulmonary sound either remained fixed or changed very slightly In 3 cases of tuberculous pericarditis the aortic second sound behaved as it does in constrictive pericarditis closing toward the R wave of the electrocardiogram early in inspiration It is suggested that these findings might provide a criterion by which cardiomyopathy may be distinguished from cardiac tamponade

I wish to thank Dr M Adams Superintendent of the King Edward VIII Hospital Durban for facilities

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Atherosclerosis in different parts of the arterial system

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It is well known that the severity of atherosclerosis may vary from one part of the vascular system to another. Thus the condition may be advanced in the coronary vessels but only slight in the cerebral vessels or vice versa. It is clear therefore that the effect of the various factors of the atherogenic pattern may vary from one part of the vascular system to another in the same individual.

This paper is concerned with possible causal factors of atherosclerosis as indicated by the severity of atherosclerosis in different arteries of the brain in relation to blood pressure and anthropometric dimensions. In addition the results are compared with those obtained in a similar investigation[1] of the coronary vessels and aorta in order to check whether the same factor differs in its effect on these three vascular areas in a given individual.

Material and methods

The study is based on the results of an investigation carried out on two series, one consisted of 94 and the other of 28 largely consecutive necropsies on adult men who died in the same hospital. Subjects with marked edema and with large operative wounds or injuries due to laceration in the areas to be studied were not accepted. In an earlier paper the diagnoses and age of the subjects were presented in detail.[1] The age distribution will be given here also: 4 men from 20 to 29 years of age, 7 from 30 to 39, 7 from 40 to 49, 15 from 50 to 59, 35 from 60 to 69, 20 from 70 to 79 and 6 from 80 to 89.

Atherosclerosis was studied in 5 cerebral vessels (Table I) and was graded in 6 stages. (1) Arteries with normal, smooth and fine intima with a clean shiny surface. Arteries with either a diffuse yellow shiny appearance or with circumscribed yellow patches without intimal thickening. (2) Arteries with focal, somewhat elevated, yellow-white to yellow plaques occurring mainly in certain sites of predilection such as bifurcations of coronary arteries, posterior wall of aorta, origin of ductus arteriosus, etc. (3) Arteries with lesions of the type described in category 2 although larger, more elevated and more numerous but nevertheless leaving a fair portion of the wall macroscopically intact. (4) Arteries with involvement of the entire intima in the segment examined in which more or less irregular, usually small, calcified foci can be felt. (5) Arteries in which plaques are only slightly ulcerated, covered with thrombi and highly calcified. (6) Arteries as in category 5 but in which the lesions are more widespread and because of their calcium content often changed into calcareous tubes or, in so far as the coronary vessels are concerned, into calcareous tubes with narrow lumina. Only if the changes were extremely advanced were the classified under this heading.

This schema, which is according to

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Table I. Severity of atherosclerosis in the given vessels

	M	±	Σ	S.D.	R
A. basilaris	1.0	±	0.10	1.06	1–5
C. a. cerebri (Willis)	3.1	±	0.10	0.96	1–5
A. cerebri post.	2.7	±	0.09	0.93	1–5
A. cerebri media	2.9	±	0.10	1.01	1–5
A. cerebri ant.	2.5	±	0.09	0.90	1–5
A. coronar. sin. desc.	3.5	±	0.11	1.10	1–6
A. coronar. sin. circ.	3.0	±	0.10	1.07	1–5
A. coronar. dx.	3.0	±	0.10	1.06	1–5
Aorta ascendens	2.6	±	0.09	0.86	1–6
Arcus aortae	3.5	±	0.08	0.88	1–6
Aorta thorac.	3.2	±	0.09	0.86	2–6
Aorta abdominalis	3.8	±	0.11	1.11	1–6

Arithmetic mean (M), error of mean (Σ), standard deviation (S.D.), and range of variation (R).

Sjovall and Wahman[10] agrees with the recommendations of the World Health Organization.[12] In the statistical treatment these grades were used without any scale correction. The same classification schema was applied to the cerebral vessels, the coronary vessels, and the aorta.

The weight of the heart was noted at necropsy. At the same time measurements were made of a number of somatic dimensions (mainly according to Lindegård[7]), namely, body weight, body length, length of radius and tibia (skeletal length factor), femoral condylar breadth (skeletal sturdiness factor), and girth of brachial biceps. In the second series the circumferences of the femoral rectus and the sartorius were also measured. The length of the radius and tibia provides a good measure of endochondral bone growth, whereas the breadth of the femoral condyle reflects appositional bone growth.[7] In addition, measurements were made of the thickness of the subcutaneous fat at three sites which are regarded as being representative of the total body fat of the individual,[4] namely, in the mid-axillary line at the level of the xiphoid process, lateral to and below the umbilicus, and at the ventral thigh above the patella. Specimens of tissue were removed from these sites and their mean cell size and cell number were determined. Readers interested in the details of the procedure, the theoretical background, and considerations on the interpretation of these fat factors are referred to Bjurulf.[1]

It should be mentioned that in the previous analysis of the correlation between atherosclerosis of the coronary vessels and body build, no correlation was made with body weight, body length, or radial length, because in that investigation interest was focused mainly on a biologic interpretation of the correlation with the total body fat.

In the statistical analysis the correlation and regression analyses were performed by conventional methods.[7,11]

Results and comments

Atherosclerosis and age. The atherosclerotic vascular changes were as a rule most advanced in the circle of Willis and least advanced in the anterior cerebral artery. The average grade of atherosclerosis of the cerebral vessels was about the same as or somewhat less than that of the coronary vessels and less than that found for all parts of the aorta, except the ascending part (Table I).

Atherosclerosis of cerebral arteries advanced markedly with age in all of the areas studied (Table II). The numerical values found for the correlations between age and severity of atherosclerosis in the various areas were roughly equal. This well-known fact that atherosclerosis increases with age has induced some authors to regard atherosclerosis as a natural phenomenon

Table II *Correlation between age and severity of atherosclerosis in given arteries*

	a basilaris	*c a cerebri*	*a cerebr post*	*a cerebr media*
Age	+0 39**	+0 51	+0 44	+0 50
	a cerebri ant		*a coron (mean)*	*aorta (mean)*
Age	+0 39		+0 43	+0 48

The significance of the correlation coefficients is indicated by asterisks. When the probability of a coefficient differing from zero was more than 99 per cent the correlation was considered to be significant (**). If the probability was less than 99 per cent but greater than 95 per cent the correlation was considered to be probable.

Table III *Comparison between severity of atherosclerosis in given arteries body weight and body length*

Atherosclerosis	*Body weight*	*Body length*
A basilaris	+0 13	−0 22
C a cerebri	+0 11	−0 27
A cerebri post	+0 20	−0 16
A cerebri media	+0 13	−0 26
A cerebri ant	+0 13	−0 10
A coronar sin d sc	+0 19	−0 14
A coronar sin circ	+0 14	−0 21
A coronar dx	+0 16	−0 21
Aorta ascendens	0 00	0 00
Arcus aortae	+0 11	0 00
Aorta thorac	+0 16	−0 06
Aorta abdominalis	+0 09	−0 06

of aging This conception has in turn given rise to nihilism concerning the possibility of preventive measures Aging per se does not cause atherosclerotic vascular changes A likely explanation is that a person is continuously or periodically exposed to special factors which produce atherosclerosis The effect of these factors will in turn cumulate and consequently increase with advancing age giving rise to advanced atherosclerosis in old age

Atherosclerosis and body build On the basis of clinical impression it has long been believed that atherosclerosis is in some way connected with body build In previous systematic investigations of the validity of this assumption interest has however been directed mainly to coronary atheromatosis For a survey of these investigations see Bjurulf[1]

This section is concerned primarily with an analysis of cerebral atherosclerosis in relation to body weight and body length the dimensions usually measured This is followed by a discussion of the fundamental morphologic body components skeleton muscle mass and fatty tissue (body fat)

In the material studied body weight showed a probably significant correlation with atherosclerosis in one cerebral artery (Table III) The probability of this numerical value being due to chance is thus one to twenty (1 20) The correlation obtained between body weight and cerebral atherosclerosis is therefore of no value as evidence No significant correlations were obtained between body weight and atherosclerosis of the coronary vessels and of the aorta (Table III) There was only one probably significant correlation among three coronary arteries and four aortic segments

Body length on the other hand was found to be negatively correlated with cerebral atherosclerosis in three of the five areas studied It is unlikely that this result is due to chance The correlation although significant is low and accounts for one sixteenth of the total variances in cerebral atherosclerosis in the series It is of interest to discuss what is the underlying biological mechanism of this statistical correlation which means that tall persons generally have less advanced atherosclerosis of the cerebral arteries than do short persons (Fig 1) Here three possible alternatives will be discussed The correlation may be due to those changes which occur in stature with advancing age Body height generally decreases somewhat with advancing age and atherosclerosis advances In this way one dimension decreases as the other incre-

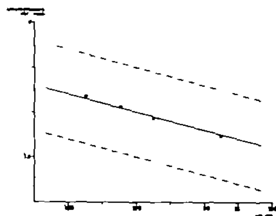


Fig 1 Correlation between body length and atherosclerosis of medial cerebral artery The taller the individual the less severe the average atherosclerosis

and thereby gives a negative correlation between stature and atherosclerosis without any causal relationship between them The results given in Table IV however argue that the correlation between stature and atherosclerosis is due to some other mechanism Here an analysis of the two factors which mainly determine body length namely skeletal length and sturdiness is carried further The skeletal length factor determines mainly the length of the limbs whereas the sturdiness factor contributes mainly to the length of the trunk The reduction that stature undergoes with increasing age cannot however be ascribed to either of these factors but mainly to increasing thoracic kyphosis and decreasing height of the intervertebral disks If the correlation were due to changes with increasing age it could thus not be ascribed to the length or sturdiness factor From Table IV it is clear however that in all cases the correlation could be ascribed to variation of the skeletal length factor Thus this suggests that the underlying biological mechanism is not due to aging phenomena

A possible alternative is that the above mentioned correlation is due to hydrostatic principles In a tall individual the column of blood to the brain is longer than in a short individual In the erect position and with the same blood pressure in the left ventricle the cerebral blood pressure should be lower in tall than in short persons This would explain the correlation provided that the lower blood pressure is combined with a less pronounced tendency to atherosclerosis But if the two correlations under discussion are compared with those of the coronary vessels the same tendencies will be found there (Table IV) Stature is negatively correlated with atherosclerosis in two of the coronary branches These two correlations can also be ascribed to variation of skeletal length which provides a basis for a biological evaluation Thus the pattern seen for coronary atherosclerosis is the same as that which was demonstrated for cerebral atherosclerosis in relation to height Furthermore in all cases these correlations can be ascribed to the length factor as represented by the radial length It is probable therefore that the same mechanism is responsible for a correlation between stature and atherosclerosis in the two regions But the hydrostatic principles postulated for the cerebral arteries cannot be applied to the coronary arteries Therefore there is no reason to assume that the correlations discussed were due to hydrostatic factors

As a third alternative one might imagine the possibility of inherited associated factors responsible for the correlation between atherosclerosis and stature This alternative is plausible because the correlation can be referred to the skeletal length factor which is primarily dependent on hereditary factors Predisposition to short stature would then be combined with predisposition to atherosclerosis of the coronary and cerebral vessels Furthermore it is apparent from the results in Table IV that there is no reason to assume that the same pathogenic factors are active in atherosclerosis of the aorta

It is well known that several authors have found a correlation between obesity and coronary atherosclerosis In the present investigation a correlation was also found between total body fat and cerebral atherosclerosis the thicker the layer of subcutaneous fat the more advanced the atherosclerosis (Table V)

The following alternatives may explain the correlation between obesity and disease in this case atherosclerosis The increase in body weight due to obesity may increase the demands on the circulatory system

Table IV. Comparison between severity of atherosclerosis in given arteries and body length, skeletal length and sturdiness factors

Atherosclerosis	*Body length*	*Radial length*	*Tibial length*	*Femoral condyle breadth*
A. basalis	−0.22	−0.21	−0.18	+0.01
C.a. cerebri	−0.22	−0.20	−0.11	−0.03
A. cerebri post.	−0.16	−0.16	−0.11	+0.12
A. cerebri media	−0.26	−0.24	−0.18	−0.06
A. cerebri ant.	−0.10	−0.11	−0.09	+0.12
A. coronar. sin. desc.	−0.14	−0.10	−0.05	+0.18
A. coronar. sin. circ.	−0.21	−0.23	−0.14	+0.07
A. coronar. dx.	−0.21	−0.23	−0.15	+0.09
Aorta ascendens	0.00	+0.12	+0.11	+0.09
Arcus aortae	0.00	+0.03	+0.03	+0.13
Aorta thorac.	−0.06	−0.04	+0.04	+0.12
Aorta abdominalis	−0.06	−0.08	−0.08	+0.07

so that mechanical factors might thus contribute to the causation of atherosclerosis. The correlation may, however, also be more complicated and be due to the intake of some atherogenic factor in proportion to the caloric supply. At the same time, since overeating results in the accumulation of fat in the body depots, one or more atherogenic substances are supplied. In this connection it is tempting to refer to the results obtained in biochemical experimental investigations by Malmros and co-workers,[8] who found that those dietary substances which consist of short-chain saturated fatty acids tend to increase the serum cholesterol level. These fatty acids are included mainly in those fats which represent a considerable portion of the calories of a normal Swedish diet. If the variations in the serum cholesterol level thus produced by exogenous factors promote atherogenesis, it would explain why body fat is correlated with atherosclerosis. As a third alternative the correlation might also be ascribed to hereditary factors of the same type as those above-mentioned ones which were presumed to be due to a correlation between body length and atherosclerosis. Then the correlation would depend on a disposition to accumulate fat combined with a hereditary tendency to develop atherosclerosis.

A guide to the evaluation of the biological implication of the correlation between fat and atherosclerosis can be obtained by examining the histologic picture of the fatty tissue and assessing the exogenous and endogenous contributions to total body fat. As shown by Bjurulf,[1] the exogenous factor, i.e. cell size, reflects mainly the nutritional state of the individual, whereas the endogenous factor, i.e. cell number, reflects the inherited tendency of the individual to accumulate fat (Fig. 2). The correlations between cerebral, coronary and aortic atherosclerosis and the different fat factors are shown in Table V.

Table V. Correlations between severity of atherosclerosis of the cerebral vessels, coronary vessels and aorta on the one hand and body fat (thickness of layer of subcutaneous fat), exogenous fat factor (cell size) and endogenous fat factor (cell number) on the other

Atherosclerosis	*Fat thickness*	*Cell size*	*Cell number*
A. basalis	0.30	0.25	0.18
C.a. cerebri	0.25	0.30	0.07
A. cerebri post.	0.32	0.23	0.24
A. cerebri media	0.31	0.26	0.21
A. cerebri ant.	0.27	0.20	0.20
A. coronar. (mean)	0.31	0.32	0.14
Aorta (mean)	0.18	0.17	0.10

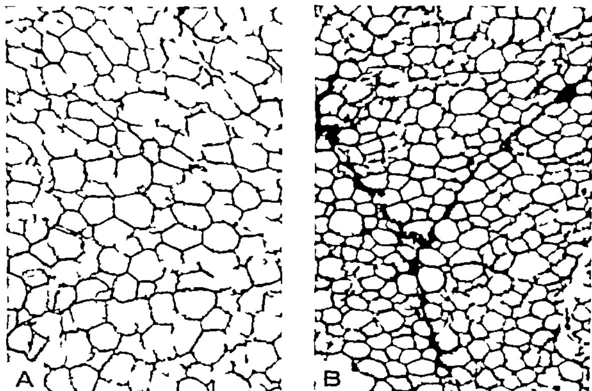


Fig. 2. Microphotographs showing subcutaneous fat tissue at the same site in two fairly obese individuals. The thicknesses of the layers of subcutaneous fat are equally large but the histologic patterns are different. In A the cells are large and few—relative dominance of exogenous fat factor—and in *B* they are rather small but numerous—relative dominance of endogenous fat factor (cf. Bjurulf[1]). (Magnification approx. ×100.)

As for coronary atherosclerosis the picture is clear. The correlation between the amount of body fat and coronary atheromatosis can be ascribed entirely to the variation in the exogenous factor, which supports the hypothesis that it is mainly the atherogenic factors in the diet that are responsible for this correlation. As for cerebral atherosclerosis, however, the results are more equivocal. In three arteries the correlation can be ascribed equally well to the two components of fat. This may be due to the possibility that neither the influence of the atherogenic factors in the diet nor common inherited determinants are of dominant importance for the correlation but only subordinate. In the light of the results obtained it is reasonable, however, to regard the correlation between atherosclerosis and the amount of fat, i.e., the total effect of exogenous and endogenous fat factors, as being of causal importance. This means that the large amount of fat in the obese person might place a strain on the circulatory system. If this assumption is correct, it would thus mean that different etiological factors are responsible for the correlation between the amount of fat and atherosclerosis of the coronary arteries on the one hand and the amount of fat and atherosclerosis of the cerebral arteries on the other. As for aortic atherosclerosis, no support could be found for a pathogenic significance to any of the fat factors discussed.

The circumference of the brachial biceps was taken as a measure of the muscle factor in the first series. In the second series three muscle circumferences were measured, namely, the brachial biceps, the femoral rectus, and sartorius, which were compared only with coronary atherosclerosis. No primary correlation could be demonstrated between the degree of cerebral or coronary atherosclerosis and the muscle circumferences. Atherosclerosis and the muscle factor, however, vary

differently with age. As mentioned previously, cerebral and coronary atherosclerosis increase with age, whereas the muscle circumferences decrease and thus masks significant correlations.

Table VI shows that after elimination of the effect of age the correlations between atherosclerosis of all the cerebral and coronary vessels and the muscle circumferences were significant. The table also shows that the same pattern of variation is obtained for cerebral atherosclerosis as for atherosclerosis of the coronary vessels when compared with the muscle factor.

In the present investigation no background was obtained for the evaluation of the correlation between cerebral and coronary atherosclerosis and the muscle factor. It would be interesting, however, to discover the biological mechanism responsible for this correlation.

In summary, significant correlations were found between the morphologic make-up of the individual and the atherosclerosis of the coronary and cerebral vessels. The patterns of variation of atherosclerosis are strikingly similar in these two areas in regard to the correlation with the skeletal length factor and the muscle factor. A tendency to a difference was found for the pattern of variation in relation to the fat factors.

No correlation was found between body build and atherosclerosis of the aorta. The findings are presented graphically in Fig. 3.

Atherosclerosis, blood pressure, and heart weight

High blood pressure is usually regarded as a considerable causal factor of atherosclerosis. But in the investigation of its significance for atherosclerosis of the coronary vessels and for coronary heart disease different results have been obtained (for references see Schettler[8]).

This section gives the results of an analysis for correlations of the clinical blood pressure and the heart weight with atherosclerosis of different vascular areas. Against the background of these data the atherogenic role played by the blood pressure will be discussed. It should be emphasized that the blood pressure noted in the clinical records does not adequately

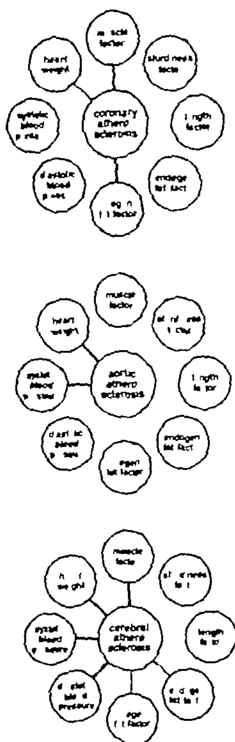


Fig. 3. Correlation between atherosclerosis in the vascular areas described, body build and exponents of the blood pressure. The bold line indicates that the correlation is significant, the thin unbroken line that it is probable, and the broken line that it is negative. Absence of connecting lines indicates absence of demonstrable correlations.

Table VI. Comparison between severity of atherosclerosis of cerebral vessels, coronary vessels and aorta on the one hand and muscle factors (circumferences of given muscles) and muscle factor independent of age on the other

I. n = 84 Atherosclerosis	Girth of biceps	
	Total	Independent of age
A. basilaris	0.21	0.38
C. a. cerebri	0.03	0.23
A. cerebri post.	0.16	0.34
A. cerebri media	0.08	0.28
A. cerebri ant.	0.16	0.32
A. coronar. (mean)	0.14	0.32
Aorta (mean)	−0.03	0.14

II. n = 28 Atherosclerosis	Biceps		Rectus femoris		Sartorius	
	Total	Independent of age	Total	Independent of age	Total	Independent of age
A. coronar. (mean)	0.10	0.40	0.10	0.48	0.17	0.38*

reflect the blood pressure of interest in this respect, i.e., the blood pressure of the individual during ordinary activity. Further sources of error due to errors in measurement, disease, and medication must also be considered. These errors are probably nonsystematic and thus reduce the numerical value for the correlation coefficients. It is not likely that these sources of errors have a greater effect on the correlation coefficient found for one vascular area than that found for another.

Some investigators have regarded heart weight as a good index of the blood pressure. There are, however, factors other than the blood pressure that influence the heart weight, such as organic valvular disease. The present material included only one patient with valvular disease, who was excluded from the calculation of the heart weight. Furthermore, heart weight is influenced by body build, mainly by muscle and fat.[1] For heart weight to reflect blood pressure, the influence of these body dimensions should be eliminated.

Table VII gives the correlations between cerebral, coronary, and aortic atherosclerosis on the one hand, and heart weight, systolic blood pressure, and diastolic blood pressure on the other. The table also includes the correlations found between atherosclerosis in the above-mentioned vascular areas and the weight of the heart independent of muscle and fat factor. The heart weight was found to be closely correlated with atherosclerosis in all of the areas studied. If the influence of body build on the correlation is eliminated, significant correlations will persist between heart weight and atherosclerosis in the cerebral vessels and in the aorta, whereas a weak tendency will persist for atherosclerosis in the coronary vessels. The systolic blood pressure shows a significant correlation with atherosclerosis of all the cerebral vessels and of two parts of the aorta. On the other hand, no correlation could be demonstrated with the atherosclerosis of the coronary vessels. Finally, the diastolic blood pressure showed a correlation with atherosclerosis of all cerebral vessels but not with atherosclerosis of any other vascular area.

It was of interest to note that the correlations between heart weight independent of body build and atherosclerosis were on the whole the same as the correlations between the systolic blood pressure and atherosclerosis. This increases the reliability of the results and suggests that the patterns of variation of the corrected heart weight and of the systolic blood pressure really reflect a factor of pathogenic relevance.

In clinical work it is widely accepted that the diastolic blood pressure better reflects the habitual blood pressure of the individual than does the systolic and that therefore treatment for hypertension is usually given according to the reaction of the diastolic blood pressure. In principle the two pressure levels show an intimate correlation—in the present investigation a close correlation (r = 0.77). However if the correlation between the systolic blood pressure and atherosclerosis is compared with the correlation between the diastolic blood pressure and atherosclerosis a systematic difference will be found. The systolic blood pressure shows throughout a higher correlation with atherosclerosis than does the diastolic blood pressure. This may be due to the fact that the above mentioned sources of error influenced the variation of the diastolic pressure more than that of the systolic blood pressure or that alternatively atherosclerosis of the aorta lowers the "Windkessel effect"—the less elastic vessel transmits the higher systolic pressure—and therefore heightens the systolic but not the diastolic blood pressure. If this explanation were correct the correlation between systolic blood pressure and atherosclerosis of the radix aortae would be high, which could not be demonstrated. However the difference may also be ascribable to the better reflection of the pathogenic factor in the systolic blood pressure.

In summary, the values found for the different measures of the blood pressure showed a strong correlation with atherosclerosis of cerebral arteries and aorta, whereas no significant correlation was found between the factors reflecting blood pressure and atherosclerosis in the coronary vessels. It should also be pointed out, however, that these results do not mean that the blood pressure is of no significance in the causation of coronary atherosclerosis. On the other hand, the results indicate that the blood pressure is of greater importance as a cause of cerebral than of coronary atherosclerosis. The findings are presented graphically in Fig. 3.

Summary

The investigation was carried out on two largely consecutive necropsy series of adult men in a large university hospital in Sweden (94 in one series and 28 in the other). The purpose was to relate atherosclerosis in different parts of the arterial system to body build and blood pressure.

Table VII. Correlation between severity of atherosclerosis in the given arteries and heart weight, systolic pressure and diastolic pressure.

Atherosclerosis	Heart weight	Heart weight independent of muscle and fat factor	Systol. blood pressure	Diastolic blood pressure
A. basilaris	0.48	0.38	0.35	0.28
Car. cerebri	0.44	0.36	0.33	0.22
A. cerebri post.	0.45	0.35	0.55	0.32
A. cerebri med. a.	0.41	0.32	0.31	0.20
A. cerebr. ant.	0.47	0.37	0.39	0.30
A. coronar. sin. desc.	0.32	0.20	0.08	0.08
A. coronar. sin. circ.	0.30	0.18	0.05	0.00
A. coronar. dx.	0.31	0.17	0.15	0.10
Aorta ascendens	0.40	0.38	0.15	0.00
Arcus aortae	0.37	0.30	0.3[illegible]	0.0
Aorta thorac.	0.28	0.26	0.17	0.07
Aorta abdominal.	0.31	0.28	0.13	0.0[illegible]

The table also includes the correlation between atherosclerosis and heart weight after elimination of the influence of the body components muscle and fat factors.

The conclusions hold of course only for these series

Cerebral atherosclerosis was found to vary with body build i e the shorter the individual the more advanced was atheromatosis of the cerebral vessels This correlation could be ascribed to the skeletal length factor (radial length) The more muscular (on the basis of the circumference of the biceps) and the fatter (thickness of subcutaneous fat at three sites) an individual the more advanced was cerebral atherosclerosis The biological background of the correlation between cerebral atherosclerosis on one hand and fat and length factors on the other was discussed Three representatives of the blood pressure (heart weight independent of muscle and fat factor systolic blood pressure and diastolic blood pressure) were all strongly correlated with cerebral atherosclerosis

Coronary atherosclerosis varied with body build in the same way as did cerebral atherosclerosis but no significant correlation was found between coronary atherosclerosis and the blood pressure

Aortic atherosclerosis varied with blood pressure but not with the body build

The findings suggest that the effect of atherogenic factors responsible for the correlation between body build as well as blood pressure and atherosclerosis varies from one vascular area to another

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Experimental and laboratory reports

An inexpensive 35 to 16-mm reduction printer and animation device for cineradiographic films

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The major disadvantage to the use of 35 mm photographic equipment in cineradiography is the cost and inconvenience of the reduction printing necessary for display on conventional 16 mm projectors. Reduction printing equipment is expensive to purchase and maintain, and commercial laboratory work is not only costly but often unsatisfactory because of unfamiliarity with radiologic standards of contrast and density. When special effects such as hold frames, superimpositions, or titles are desired, commercial laboratories with specialized equipment must be consulted at prohibitive expense.

This communication describes a modification of a commonly used 35 mm analytical projector which permits inexpensive reduction printing to 16 or 8 mm film as well as inclusion of a variety of special effects.

Materials

A 35 mm analytical projector viewer is coupled with a 16 mm motion picture camera as shown in Fig. 1. Synchronization of the camera and projector is effected by a photorelay activated by the projector beam. As each individual frame of 35 mm film is projected through the rotating prism of the projector at 1 or 2 fps, the photorelay immediately below the image

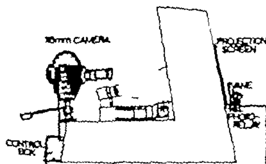


Fig. 1. Diagram of reduction printer. A 16-mm motion picture camera is rigidly mounted to the frame of a 35 mm analytical viewer (Tage Arno RG 35) and the lens is focused on the projection screen. A 35 mm cineradiographic film is projected on the screen at a rate of 1 or 2 frames per second. The flashing light from each individual frame stimulates the photorelay below the projection screen, which in turn activates the single frame release of the 16 mm copy camera. Hold frame effects can be achieved by stopping the transport of the cineradiographic film and activating the vane which rotates slowly and interrupts the light beam in a manner simulating continuous running of the 35 mm film.

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Fig. 2. Technique of superimposition. Diagrams and titles can be superimposed on cineradiographic film by projecting the film on matte paper containing the diagram. *Top*: The analytical projector has been stopped on the desired frame and the 16-mm. camera inactivated. Note the small hole beneath the white projection screen through which the photorelay is stimulated. *Bottom*: A diagram made with India ink on matte typewriter paper is inserted in registration with the cineradiograph. The [illegible] (see Fig. 1) is then activated and multiple exposures of the superimposition will be taken.

on the screen activates the single frame release of the 16 mm camera. If the projector is stopped on a frame, multiple 16 mm exposures (hold frame effect) may be made by interrupting the light beam below the image area with a rotating vane. Identifying labels, diagrams or arrows may be superimposed by inserting 8½ by 11 matte paper appropriately marked with India ink in registration with the projection screen (Fig. 2). The image projected on the paper is copied with the 16 mm camera so that the superimposition is effected with a single exposure.

Introductory titles can be prepared with a standard typewriter illuminated by the projector bulb and copied in sequence with the cineradiograph. The resulting 16 mm print will thus have titles, diagrams, etc., without splices.

Technical data

A model RG 35 Tage Arnø analytical projector is utilized without modification of the projector bulb, screen, or optical system. A 16 mm Bell and Howell 70 E camera with an Angenieux Zoom lens (17–68 mm) and +2 Portra attachment is rigidly mounted on the projector frame. A tripod pan head is used to allow flexibility in composition. A 3/8 inch hole is drilled immediately below the white projection screen in the area of the interframe line of the projected image, and a photorelay (Sigma 8 RCO2 A) is mounted behind the hole. A small 60 r.p.m. synchronous motor with a 2 blade vane is mounted between the hole and the photocell so that the fan blade will interrupt the beam of light projected through the hole two times a second for multiple exposures of a single frame.

The photorelay is connected through appropriate circuitry (Fig. 3) to a single frame release on the 16 mm camera, permitting the camera to expose only one frame of film when the photorelay is exposed to light. An interruption of the light beam occurs with transport of the 35 mm film in the projector or when the 60 r.p.m. motor is activated with a single frame on the screen for hold frame effect.

A frame counter and timer for the vane motor are included in the control box, as well as a main power switch, a single frame tripper and a switch to inactivate the photorelay.

Kodak Double X negative film is used

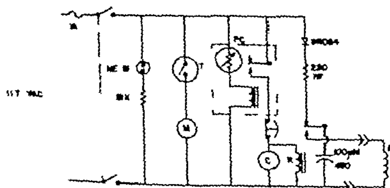


Fig. 3. Circuit diagram which indicates the components used in the authors' apparatus. It is offered as a rough guide only, since different cameras require different types of single frame activation. Light falling on the photorelay (*PC*) closes the switch and activates a solenoid (*S*) attached to the camera through an appropriate relay (*R*) and capacitor. A photographic time switch (*T*) can be used to activate the vane motor (*M*) for measured hold frame effects. A counter (*C*) records the number of 16 mm frames exposed. Manual exposures can be made by pushing and releasing the push button immediately above the counter. The photorelay contacts must be closed by a properly centered 35 mm frame or the manual switch will not operate. List of components: relay (*R*) 115 V AC Advance GHP/1c/115 AC; photorelay (*PC*) Sigma 8 RCO2 A; photographic time switch (*T*) 0–120 sec.; vane motor (*M*) 60 r.p.m.

in the 16-mm. camera allowing an exposure of 1/16 of a second at f/2 to f/8, depending on the density of the film to be copied. Average-density cineradiographs require f/4, whereas underexposed or overexposed original films can be adequately copied by adjustment of aperture. The film is developed in a Picker-Smith processor with Ethol 90 developer for 4 minutes at 65°F, which is the same processing utilized for the original cineradiographs. The zoom lens is utilized to copy titles printed with a typewriter and allows flexibility in composition without changing the camera-to-screen distance. A zoom close-up is utilized to emphasize a small detail in a cineradiographic sequence.

Results

The 16-mm. reduction prints compare quite favorably with commercially made films and have the advantage of splice-free titles, superimpositions, and animations. The graininess of the prints despite the use of high-speed film (necessary because of the low intensity projector bulb) is not objectionable. Resolution of detailed structures such as small branches of coronary arteries is excellent. The wide gray scale of the film obviates the excessive contrast that characterizes copied films.

Discussion

Cineradiographic films are useful in the teaching of students and residents, in addition to being of obvious value in diagnosis and research. To the uninitiated, however, comprehension of rapid motion pictures of unfamiliar structures is often limited. Thus, the ability to produce inexpensive reduction prints with identifying titles and diagrams designed for continuous projection in conventional projectors is especially advantageous.

In our laboratory, studies on the origin of heart sounds and pressure pulses by cineangiography[1-4] proved to be quite cumbersome to report to scientific meetings because of the necessary detailed analysis and correlation of motion pictures and oscillographic data. Through utilization of this system of reduction printing, the actual recordings of pressure and sound could be superimposed on the 16-mm. prints using the technique shown in Fig. 2.

Summary

A simplified, low-cost method for reproducing 35 mm. cineradiographs on 16-mm. film with inclusion of titles and superimpositions is described. A commonly used analytical projector has been coupled and synchronized with a 16-mm. motion picture camera, and the 16-mm. film can be processed in the same manner as the cineradiographs. The system is especially useful for preparing films for the teaching of students and residents as well as for presentation of complex analyses of cineradiographs.

The authors gratefully acknowledge the technical assistance of Mrs. Christa Kaelber and Mr. Richard Hiner.

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Effects of several cardiovascular drugs* on various phases of circulatory dynamics

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Although the value of sympathomimetic amines in the treatment of shock has been recognized for some time, the agents chosen may not always be the most efficacious available. The purpose of this study was to delineate the action of certain drugs which affect the cardiovascular system so as to provide a better basis for the selection of the agent most suitable for a particular clinical situation. The literature contains many reports of experimental and clinical findings concerning the drugs used in this study, but, to my knowledge, there are no reported studies in which these compounds were compared with one another in the same animal with particular reference to the simultaneous effect on the various parameters monitored in this study.

The information presented is not intended to be entirely new; however, it is in part a review intended to contribute to an understanding of how and why drugs of the type used in this study produce their pharmacodynamic effect on the cardiovascular system.

After the administration of a drug with conspicuous cardiovascular effects, the changes in circulatory dynamics are dependent on the direct effect of the drug and the reflex homeostatic response to the drug. In man, epinephrine causes an increase in cardiac output, whereas levarterenol may cause a decrease.[1] Guyton and associates[2] have shown that epinephrine increases cardiac output by increasing mean circulatory pressure which in turn increases the pressure gradient forcing blood toward the right atrium. Collier and associates[3] further defined the increase in cardiac output which occurs with epinephrine in dogs, but found that levarterenol usually decreases cardiac output or causes no change. Gorten and associates[4] have shown that isoproterenol increases cardiac output approximately 33 per cent in man.

Each drug used in the present study invariably produced characteristic directional changes in blood pressure and myocardial contractile force, although the magnitude of these changes varied. On the other hand, changes in output were recognizably the result of several parameters.

Methods

These experiments were conducted in 38 open-chest dogs which weighed between 8 and 14 kilograms. Anesthesia was attained with 30 mg. per kilogram of sodium

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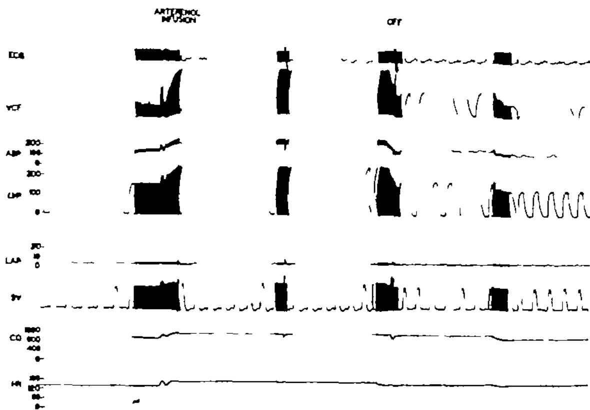


Fig. 1. The effects of arterenol on the cardiovascular system. ECG, Electrocardiogram. VCF, Right ventricular contractile force. ABP, Aortic blood pressure (mm. Hg). LVP, Left ventricular pressure (mm. Hg). LAP, Left atrial pressure (mm. Hg). SV, Stroke velocity. CO, Aortic flow (c.c./min.). HR, Heart rate. Paper speed of 2.5 and 25 mm. per second with each vertical space between lines representing 0.2 second at the faster speed.

pentobarbital intravenously. Light surgical anesthesia was maintained with small subsequent doses periodically. Aortic flow (CO), *ventricular contractile force (VCF)*, heart rate (HR), and aortic blood pressure (ABP), and in some experiments velocity of aortic ejection or stroke velocity (SV), electrocardiographic Lead II (ECG), right (RAP) and left (LAP) atrial and left ventricular (LVP) pressures were measured and recorded. The right femoral artery and vein were cannulated with PE 190 polyethylene tubing. The arterial cannula was inserted into the aorta to the level of the diaphragm for the measurement of ABP, and the venous cannula was inserted 5 or 6 centimeters into the inferior vena cava for administration of the drug. After a tracheotomy, the animals were intubated and ventilated mechanically with a Harvard *respirator using room air*. A mid-sternal thoracotomy was performed and VCF, CO, SV, RAP, LAP, and LVP were measured. A strain gauge arch was sutured to the right ventricle.[3,4] The sutures for attachment of the strain gauge were *placed approximately 20 mm. apart*. When the arch was attached to the ventricle, the muscle between the two legs of attachment were thus stretched by approximately 30 per cent of the end diastolic length. Therefore, the recording of myocardial adjustments secondary to changes in total peripheral resistance and heart rate were minimal because of the extended initial length of the muscle segment. The changes measured in VCF have been shown to be primarily due to humoral and neurogenic factors.[7,8] In the present experiments, right VCF was measured. It has been shown that changes in VCF which are recorded from any given area of either ventricle are representative of changes in the entire heart.[7] Atrial and ventricular pressures were measured from cannulas inserted directly into the atrial and ventricular

chambers and held in place with purse string sutures Statham transducers (P23 D) were used to measure all changes in pressure SV and CO were measured with a square wave electromagnetic flow meter[8,11] HR was measured with a tachometer All changes in BP HR CO SV and VCF were recorded on an 8-channel Grass polygraph

The five drugs listed below were administered to each animal The time period between the administration of each drug was 15 minutes with the longer acting methoxamine given last In all cases the animal had returned to control levels prior to injection of the next drug

Levarterenol and epinephrine were infused in a 001 per cent solution (10 micrograms per cubic centimeter) at a rate of 2 micrograms per kilogram per minute for 2 minutes

Isoproterenol was infused in a 00025 per cent solution (2 5 micrograms per cubic centimeter) at a rate of 5 micrograms per kilogram per minute for 2 minutes

Methoxamine was infused in a 1 per cent solution (1 milligram per cubic centimeter) at a rate of 2 milligrams per kilogram per minute for 2 minutes

Nitroglycerin was administered in a single injection of 05 milligrams per kilogram

Results

Levarterenol (Levophed) The changes in the parameters shown in Fig 1 are typical There was a pronounced increase in myocardial contractile force aortic blood pressure and left ventricular pressure with *an increase in the velocity of systolic* ejection There was only a slight increase in cardiac output and thus appeared to be the result of augmented heart rate rather than increased stroke volume ECG changes consisted of T wave reversal accompanied by a slightly increased S T depression There was little change in left atrial pressure

Levarterenol often causes a reflex bradycardia because of the increase in peripheral resistance Fig 2 shows the effect of mid cervical vagotomy on this type of response With intact vagi a reflex bradycardia causes a marked decrease in cardiac output After section of the vagi heart rate increased with a consequent rise in cardiac output

Epinephrine Epinephrine produces approximately the same changes in VCF LVP and ECG as those which occur with levarterenol (Fig 3) The pressor action of epinephrine is generally less than that of levarterenol and epinephrine produces less reflex bradycardia therefore the direct sympathomimetic effect of epineph

*Table 1 Summary of results in 3? experiments**

Parameter	Levarterenol		Epinephrine		Isoproterenol		Methoxamine		Nitroglycerin	
	Per cent	S D	Per cent	S D	Per cent	S D	Per cent	S D	Per cent	S D
CO	+39	±27	+38	±32	+30	±23	−44	±43	+16	±1
VCF	+147	±72	+141	±26	+184	±87	−10	±19	−1	±6
SBP	+71	±50	+61	±21	−33	±16	+96	±40	+14	±30
DBP	+85	±32	+60	±28	−42	±11	+90	±1	−49	±70
HR	−6	±19	+12	±17	+31	±11	−79	±1	−4	±8
TPR†	+50		+16		−52		+244		+16	±6
									−55	

Control heart rate 136 beats min, SD ± 33

Control blood pressure $\frac{114 \text{ SD} \pm 3}{87 \quad \pm 21}$ mm Hg

*Per cent changes from control values in cardiac output (CO) ventricular contractile force (VCF) systolic blood pressure (SBP) diastolic blood pressure (DBP) heart rate (HR) and total peripheral resistance (TPR) which occurred during administration of the indicated drug

†TPR = $\frac{\text{Mean aortic blood pressure}}{\text{Cardiac output}}$

‡Nitroglycerin produced an initial increment in CO (14 per cent) which was always followed by a decrease (31 per cent)

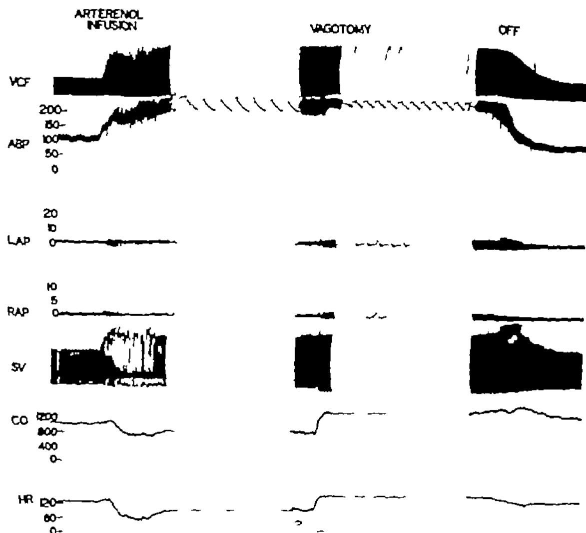


Fig 2 The effect of vagotomy on the cardiovascular response to arterenol *RAP* Right atrial pressure (mm Hg) Other symbols are the same as in Fig 1 Removal of vagal tone produced a marked increment in CO

rine on heart rate is more apparent than that of levarterenol The increment in total peripheral resistance is usually less than that which occurs with levarterenol and this coupled with changes in heart rate is responsible for the greater increase in cardiac output produced by epinephrine

Isoproterenol Isoproterenol is a vasodilator and in addition has a powerful positive inotropic effect similar to that of levarterenol and epinephrine[11] This drug also produces a positive chronotropic effect (Fig 4) which may be attributed to its direct action as well as the reflex response of the pressor receptors to hypotension The left ventricular systolic pressure is usually higher than the aortic systolic pressure and appears to be related directly to the velocity of development of tension The rise in ventricular pressure after the aortic valves open is 75 mm Hg as compared to aortic pulse pressure of 35 mm Hg This may be due to the marked increase in the velocity of development of myocardial tension and force of contraction In addition the increased peripheral runoff of blood from the aorta consequent to the vasodilating action of isoproterenol may contribute to this pressure differential During infusion of isoproterenol there was approximately a 100 per cent increase in isometric tension (VCF) prior to and after

valvular opening even though there was a marked decrease in peripheral resistance. It is interesting to note the ventricular extrasystole at the right in Fig. 4. This ectopic beat produced an adequate increase in myocardial isometric systolic tension or potential contractile force. However, the prematurity of contraction, inadequate ventricular filling, and increase in diastolic pressure prevented ejection of blood during systole. On the contrary, the beat which followed the extrasystole produced an increase in stroke velocity and volume due to the prolongation of diastole, causing an increase in ventricular filling and a decrease in resistance to systolic ejection.

Methoxamine (Vasoxyl). Fig. 5 is an illustration of the cardiovascular effect of methoxamine. Methoxamine is primarily a vasopressor agent which has little direct effect on the myocardium.[12] The increment in peripheral resistance causes a decrease in ventricular tension available to perform external work, which is accompanied by a decrease in stroke velocity and volume. Fig. 6 shows the effect of relieving the myocardial work load produced by methoxamine. Nitroglycerin reduced the pressure work load and reflex vagal tone, thereby causing cardiac output to increase three-fold.

Nitroglycerin. Fig. 7 represents typical cardiovascular effects of nitroglycerin, a drug which has a direct vasodilator action.[13,14] The fall in blood pressure causes a reflex sympathoadrenal release and a decrease in vagal tone in an attempt to maintain homeostasis. The slight increase in contractile force may be partially attributed to an increment in coronary flow as well as reflex sympathetic activity. Changes in the ECG and left atrial pressure were negligible. Usually, there was an initial increase in cardiac output followed by a prolonged decrease. All results are summarized in Table I.

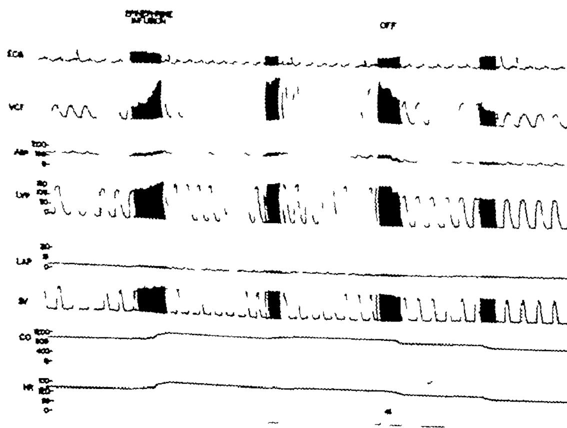


Fig. 3. The effects of epinephrine on the cardiovascular system. Symbols are the same as in Fig. 1.

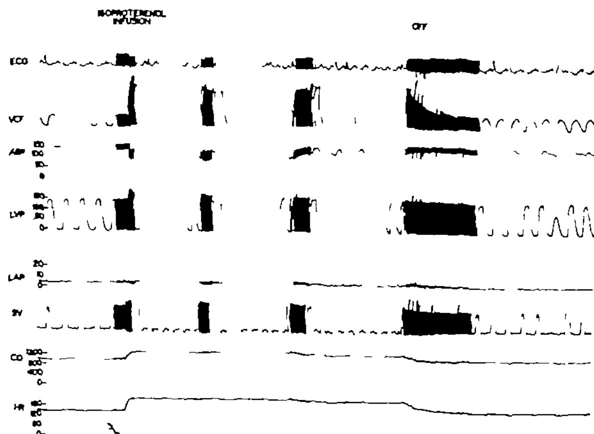


Fig. 4. The effect of isoproterenol on the cardiovascular system. Symbols are the same as in Fig. 1.

Discussion

Normal cardiovascular activity is the result of a balance between the excitatory and inhibitory influence of the autonomic nervous system, and during deviations away from the normal this system attempts to maintain homeostasis. Of prime importance in these studies was the ability of the myocardium to increase its pumping capacity in the face of abnormally high work loads. Drugs which stimulated myocardial contractility, such as epinephrine and levarterenol, were able to overcome large increases in total peripheral resistance. Vasopressor drugs which produced little inotropic effect, such as methoxamine, markedly increased total peripheral resistance, producing a reflex bradycardia and resistance to systolic ejection which so altered stroke volume and heart rate that cardiac output was significantly decreased.

Stroke volume is dependent upon the length of diastole, effective filling pressure, aortic blood pressure, ventricular distensibility, ventricular contractile force, and venous return. There was little change in the left atrial pressure during all drug responses, and methoxamine was the only drug which consistently increased diastolic filling time. Positive inotropic vasopressor drugs produced either no change or a slight increase in stroke volume, which may be attributed to an increase in ventricular contractile force and velocity of systolic ejection. There was also an increase in the rate of ventricular relaxation. Brewster and associates[15] have reported that the rate of myocardial relaxation is directly related to the rate of metabolism, the active transfer of chemical bond energy occurring during relaxation. With the administration of epinephrine, levarterenol, and isoproterenol, the angle between the slope of the relaxation curve and the base line approaches 90 degrees, which suggests

an increase in the rate of myocardial metabolism. Rushmer[18] found that end diastolic ventricular diameter and circumference was increased by epinephrine and levarternol. In the present experiments the slight rise in the VCF base line which occurred during drug response indicates a change in length tension relationship not due to changes in heart size. Since VCF was measured with the strain gauge arch at a fixed length, the recorded changes in VCF are primarily a result of intrinsic changes rather than cardiac size or extrinsic changes.[7, 8] This is not to say that these changes in force are not occurring; however, the recording of these changes are minimal if one considers the initial stretch on the segment of muscle under measurement. Szent-Gyorgyi[17] states that isometric contraction is a measure of the maximum working capacity of muscle and depends on free energy change or that portion of total energy available for the performance of work. Prolonged infusion of positive inotropic drugs appears to gradually deplete stored energy available for cardiac work. Olson and Piatnek[14] divide the metabolic processes in heart muscle into three general phases, i.e., liberation, conservation, and utilization of energy. It seems likely that an increase in the liberation and utilization of energy and a decrease in the conservation of energy would accompany the free energy change which occurs with an increment in myocardial contractility and would depend on a faster rate of utilization than of liberation of energy. This may contribute to the decreased cardiac response which sometimes occurs during prolonged administration of drugs.

The administration of nitroglycerin is followed promptly by a short-lived increase in cardiac output. Subsequently, cardiac output decreases, probably because of a decrease in venous return which accompanies the progressive pooling of blood in the periphery. There appeared to be little change in the myocardial free energy release as indicated by an almost constant amplitude of ventricular contraction. The rate of metabolism was not altered significantly, as indicated by the slopes of the ventricular tension curves.

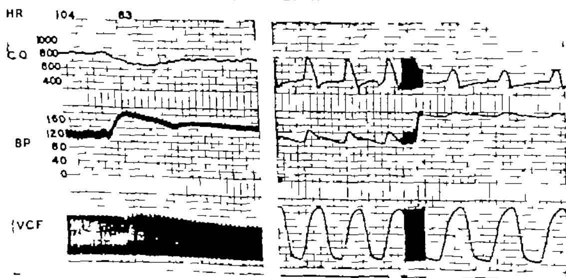


Fig. 5. The effect of methoxamine (Vasoxyl) on the cardiovascular system. Symbols are the same as in Fig. 1. Paper speed of 25 and 50 mm. per second. The top tracing on the right is stroke velocity. After the administration of methoxamine an increase in myocardial tension (VCF) is necessary to overcome the increase in resistance to systolic ejection, which is indicated by the changes in CO and SV. Therefore, the available VCF for the performance of external work (blood ejection) is markedly reduced.

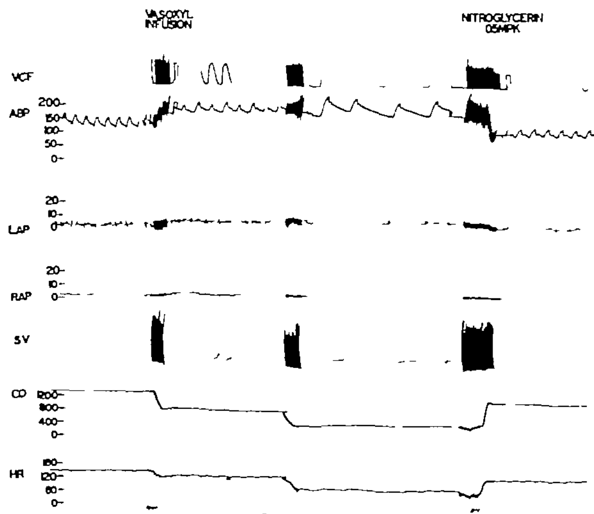


Fig. 6. Effect of nitroglycerin on hypertension induced by Vasoxyl. *RAP*, Right atrial pressure (mm. Hg). Other symbols are the same as in Fig. 1. After infusion of Vasoxyl the third and fourth ejection in the *SV* tracing were not recorded due to malfunction of the ink pen. This is not a pulse deficit; however, the third *VCF* curve prior to the administration of nitroglycerin does produce a pulse deficit. The decrease in cardiac work load and reflex increase in heart rate produced by nitroglycerin during infusion of Vasoxyl caused a marked increment in *CO* and the return of a regular cardiac rhythm.

The administration of nitroglycerin during infusion of methoxamine decreased blood pressure to near control levels and abolished the reflex bradycardia, with a consequent decrease in stroke work and an increase in cardiac output. Vagotomy during infusion of levarterenol with reflex bradycardia produced similar results. It has been shown in this laboratory that nitroglycerin has no intrinsic effect on the increased force of contraction elicited by arterenol; however, it does decrease myocardial contractility by decreasing the hemodynamic work load.[19]

Of the drugs used in these experiments, isoproterenol produced the largest increment in VCF and heart rate. The increase in VCF is due to the direct inotropic effect of the drug, whereas the effect on heart rate is attributable to the direct effect of the drug and to reflex action secondary to hypotension. These changes in VCF and heart rate resulted in an increase in cardiac output. Of particular interest was the effect of isoproterenol on the left ventricular blood pressure as contrasted with its effect on aortic blood pressure. Generally, ventricular systolic pressure was

greater than aortic systolic pressure during the drug response. This may be attributed to a combination of an increase in the magnitude and velocity of development of myocardial tension, if one considers the limited size of the ventricular aortic orifice, as well as to an increase in peripheral run off of blood from the arterial system. Krasnow and associates[8] have related this marked pressure gradient which occurs with isoproterenol to obstruction of the ventricular outflow tract.

A good correlation between several parameters affecting cardiac output is evident when a comparison is made between drugs which produce varied responses of VCF, heart rate, and blood pressure. For instance, methoxamine produced a marked decrease in cardiac output which may be attributed to the increased peripheral resistance and reflex bradycardia. On the other hand, levarterenol produced an increase in cardiac output due to its ability to increase myocardial tension to such a degree as to overcome the increased pressure work load. Also the positive inotropic and chronotropic effects of isoproterenol, as compared to nitroglycerin, were able to increase cardiac output. These results agree with ballistocardiographic evidence of similar changes in both dogs and human subjects after the administration of sympathomimetic amines and nitroglycerin.[11,1]

The effects of these drugs on coronary flow have been reported previously.[7] Since heart muscle extracts an almost maximal amount of oxygen under normal conditions, the coronary flow is the first line of defense against increased cardiac load. Regardless of the direct action of drugs on the coronary vessels, induced changes in cardiac tension and myocardial metabolism are largely responsible for changes in coronary vascular tone. Myocardial oxygen utilization appears to be associated primarily with myocardial tension rather than external work.

Shock is usually accompanied by derangements of acid base which further complicate cardiovascular drug response. The cardiovascular response to epineph

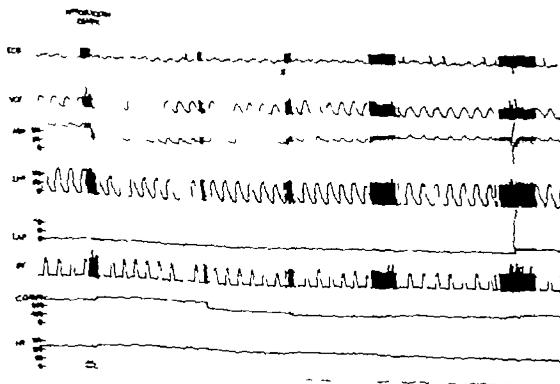


Fig. 7. Effect of nitroglycerin on the cardiovascular system. Symbols are the same as in Fig. 1.

rine and levarterenol prior to and after treatment of metabolic[19, 24] and respiratory[24] acidosis have been reported During acidosis the cardiovascular system is relatively refractory to levarterenol and epinephrine However after normal pH is restored drug responsiveness returns toward normal Also it has been shown that the use of other sympathomimetic amines may be of value in shock which is refractory to levarterenol[4] Dogs whose shock had become nonresponsive to levarterenol were given mephentermine (Wyamine) metaraminol (Aramine) or ephedrine Increased myocardial contractility and a pressor response occurred however when refractoriness to these agents developed it was found that responsiveness to levarterenol had returned in many instances

The value of positive inotropic drugs in shock accompanying myocardial infarction[11, 7] and all pressor drugs in the support of blood pressure during hypotension has been reported[23] However blood flow rather than blood pressure is responsible for the oxygenation of and the removal of metabolites from tissue Therefore in shock associated with cardiac depression the use of pure vasopressor drugs may increase cardiac work load and further aggravate the hypodynamic heart although they may be of value in low spinal shock not associated with myocardial depression

Summary

This study shows some of the cardiovascular parameters which can influence cardiac output, all of which are in operation simultaneously Changes in cardiac output were inconsistent although each drug invariably produced characteristic directional changes in blood pressure and ventricular contractile force During the administration of drugs the reflex response to cardiovascular changes were of prime concern in the regulation of cardiac output The algebraic sum of the drug effect and the reflex homeostatic response to the drug determines the end changes in cardiovascular dynamics Therefore directional changes in cardiac output cannot always be categorically stated The pressor drugs (epinephrine and levarterenol) which have a positive inotropic action usually produced an increment in cardiac output even though there was an increase in peripheral resistance to systolic ejection The pressor drug methoxamine which has little or no cardiac action always produced a decrease in cardiac output consequent to the marked increase in peripheral resistance and reflex bradycardia Nitroglycerin a vasodilator with little cardiac action decreased cardiac output associated with progressive peripheral pooling of blood however isoproterenol a vasodilator with marked positive inotropic action always produced an increment in cardiac output as a result of increased myocardial contractility and heart rate Indeed the value of pressor inotropic drugs over pressor drugs as supportive measures in shock therapy cannot be overemphasized

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Myocardial blood flow after experimental pulmonary embolism in the intact dog

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Sudden death in pulmonary embolism has been attributed to interference with the supply of blood to the heart.[1] It has been suggested that reflexes mediated through the vagus nerves were elicited by the presence of small emboli in the lung obstructing and distending the pulmonary arteries and causing a widespread *reflex pulmonary arteriolar and coronary* constriction. Thus the precordial pain and electrocardiographic pattern compatible with acute coronary insufficiency observed after pulmonary embolism were attributed to such coronary vasoconstriction.[2-4] Anatomic studies in some patients dying of pulmonary embolism showed acute myocardial changes possibly as a *result of coronary insufficiency.*[4] Furthermore, in experimental pulmonary embolism focal areas of necrosis have been found in the right ventricle.[5]

In the light of these clinical and anatomic observations, quantitative measurement of coronary blood flow after pulmonary embolism or sudden increase in right ventricular pressure has been studied extensively. The results of the experimental investigation have yielded conflicting views.

Katz and associates,[6] using heart-lung and isolated heart preparations, found that an increase in the load of the right ventricle due to elevation of the intraventricular pressure caused a decreased flow in the right coronary artery. Visscher,[7] using a special heart-lung preparation, presented evidence that elevation of the *pulmonary arterial pressure* caused a diminution in extracoronary sinus drainage into the right heart. On the other hand, Gregg[8] found an increase in coronary inflow after a sudden increase in right ventricular pressure. Hackel and associates[9] studied the effects of pulmonary embolism on coronary sinus outflow (in the intact anesthetized dog) utilizing the nitrous-oxide method. They found *no* significant change in the rate of coronary outflow after pulmonary embolism, although the mean pulmonary arterial pressure was tripled.

In recent years the radioactive isotope of rubidium (Rb^{86}) has been used to assess the rate of myocardial blood flow.[10, 11] This method has been utilized to determine the blood flow in the various regions of the myocardium. In the present experi-

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ments the coronary circulation of the different areas of the right and left ventricles were studied in intact anesthetized dogs after pulmonary embolism We hoped that this experimental approach would help clarify the divergent findings observed on the coronary vascular response cited above

Methods

Experiments were performed on 28 mongrel dogs which ranged in weight between 9 and 16 kilograms and which were premedicated with morphine sulfate (2 mg per kilogram) and anesthetized with 0 25 ml per kilogram of a mixture of equal volume of Dial urethane and pentobarbital sodium Systemic blood pressure was measured by way of a polyethylene catheter inserted into a femoral artery The other femoral artery was used for intermittent sampling of arterial blood Catheterization of the right side of the heart was done under fluoroscopic guidance via the jugular vein and the cardiac catheter was advanced to either the right or the left pulmonary artery A Grass polygraph machine was employed to record simultaneously the arterial and pulmonary blood pressures and the electrocardiogram (Leads II and aV_F) In 15 dogs pulmonary embolism was accomplished using 5 per cent starch solution (2 5 to 3 ml per kilogram) introduced through the cardiac catheter the amount of starch solution given was adjusted so as to produce persistent pulmonary hypertension Samples of arterial blood were obtained anaerobically before and immediately after pulmonary embolization for analysis of oxygen content using the method of Peters and Van Slyke [22]

After the animal was heparinized (3 mg per kilogram myocardial Rb^{86} clearance was determined according to the method previously described [23] Briefly this consisted of infusing 7 5 c c of Rb^{86} chloride (approximately 80 to 100 μc with specific activity of 1 24 to 1 75 μc per milligram) by way of the jugular vein Samples of arterial blood were collected at 10 second interval for isotope assay At the end of exactly 1 minute the infusion was stopped and the animal was killed by electric shock with electrodes applied on the precordial area The heart was immediately taken out of the chest washed with tap water and blotted dry and myocardial samples were taken at different areas as shown in Fig 1 The Rb^{86} content of the blood and tissue specimens were determined in a well type scintillation counter Rb^{86} clearance was calculated by dividing the average tissue content of this isotope (CPM per gram of myocardium) by the mean blood content (in CPM per gram of blood)

Results

Of the 28 experiment performed 8 were not included in the analysis for the following reasons (a) in 1 the hemoglobin and hematocrit values were low (b) in 6 systemic hypotension developed after pul

Table I Comparative table of hemoglobin hematocrit and hemodynamic data in 20 experiments

	Control			Pulmonary embolization					
				Pre embolization			Postembolization		
	Mean	±	S D	Mean	±	S D	Mean	±	S D
Hemoglobin (Gm %)	9 6		0 99	10 90		1 6	—		—
Hematocrit	33 3		2 40	38 70		5 20	—		—
Heart rate per min	95 7		6 19	98		15 36	106 4		26 12
SBP (mm Hg)	142 5		16 40	143		14 40	141 6		16 60
PAP (mm Hg)	—		—	14 3		2 73	30 8		4 21

SBP Systemic blood pressure PAP Pulmonary [illegible] pressure The [illegible] of the [illegible] 106 4 ± 8 27 (S E) > 98 ± 4 86 (S E) [illegible] p > 0 05 [illegible] blood pressure [illegible] 143 ± 4 36 (S E) > 141 ± 5 23 (S E) of the pre-embol[illegible] p > 0 05

monary embolization and (c) in 1 there was a delay in taking out the heart after the end of the Rb^{84} infusion. The results of the 20 experiments to be reported showed a comparable hemoglobin, hematocrit, systemic blood pressure, and heart rate (Table I). After pulmonary embolization with starch solution, a sustained pulmonary hypertension developed within 2 or 3 minutes. The degree of elevation of the pulmonary arterial pressure ranged from 17 to 150 per cent of the control. During this pulmonary hypertensive state there was no significant difference between the pre-embolization and postembolization heart rate and systemic blood pressure (Table I). Rb^{84} clearance was determined during this period. In the 8 experiments in which arterial blood gas analyses were done, the blood oxygen contents before and after pulmonary embolism did not vary significantly. In 5 pulmonary embolization experiments myocardial tissue was homogenized and tested for the presence of starch granules. The iodine test for starch was negative in all the myocardial samples.

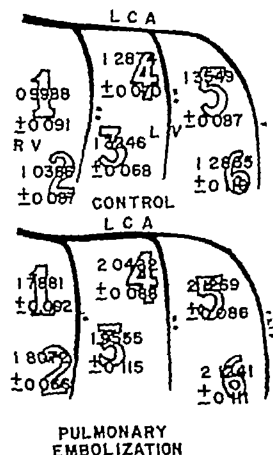


Fig. 1. Myocardial distribution of Rb^{84} clearances in the control and pulmonary-embolized dogs. The large numbers represent the myocardial regions with their mean Rb^{84} clearances and ±S.E. Regions 1 and 2 are in the central and septal areas of the right ventricle, respectively. Regions 3 to 6 are located on the left ventricle: region 3 along the anterior descending branch, regions 4 and 5 in the basal portion, and region 6 at the apex. The major branches of the left coronary artery shown are: left circumflex artery (*l.c.a.*), anterior descending artery (*a.d.a.*), ramus marginis obtusi (*r.m.o.*), and ramus sulci longitudinalis posterioris (*r.s.l.p.*).

The Rb^{84} clearances of the different myocardial regions in the control and pulmonary-embolized dogs are presented in Table II. The distribution of the different myocardial zones for the mean Rb^{84} clearance values is shown in Fig. 1. A bar graph (Fig. 2) shows the comparative picture of the mean Rb^{84} clearance of myocardial zones presented in Fig. 1 for both control and pulmonary embolized dogs. Each pair of bars represents mean Rb^{84} clearance ± the standard error obtained from 20 experiments. The results show that the mean myocardial Rb^{84} clearance of pulmonary-embolized dogs was significantly greater than that of the corresponding control in all 6 different myocardial zones (Fig. 2). The total mean Rb^{84} clearance of the right ventricle (regions 1 and 2) in in pulmonary-embolized dogs was significantly higher than in the control animals ($p < .0001$). Likewise, in the left ventricle (regions 3 to 6) the difference between the total mean Rb^{84} clearance of pulmonary-embolized dogs and the controls was significant ($p < .0001$).

Discussion

The result of our study shows a statistically significant increase in blood flow in all the regions of the coronary circulation after pulmonary embolization. Since the increase in coronary blood flow during the pulmonary hypertensive state is not associated with any elevation in the systemic blood pressure nor significant increase in heart rate, this would indicate a widespread coronary vasodilation. This observation is in agreement with studies made by Cross[14] on the response of the coronary vascular bed after pulmonary hypertension in

which she observed a diminished vasomotor tonus in both the right and left coronary vascular trees In the present study the coronary vascular response elicited must be explained on the basis of factors other than arterial oxygen desaturation since no significant difference was established between the pre-embolization and post embolization values of oxygen in the arterial blood Whatever is the specific mechanism involved it is most likely a compensatory response to keep up the supply of oxygen at the myocardial tissue level in proportion to the demand This is based on the direct relationship between the tension time index and oxygen consumption of the myocardium[14] With pulmonary arterial embolization and the subsequent increase in pulmonary vascular resistance the right ventricular pressure and therefore the tension time index are increased creating a greater demand for oxygen This increased consumption of oxygen must then be met by a greater coronary blood flow or increased tissue extraction of oxygen from the coronary arterial blood Any disproportion between the oxygen demand and supply in excess of the former will create a state of myocardial hypoxia which may result in necrosis despite an absolute increase in coronary blood flow

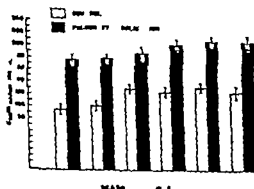


Fig 2 Bar graph of Rb clearances in ml /min /100 Gm for the 6 myocardial regions designated in Fig 1 for control The white bars represent the controls and the black bars represent the pulmonary embolized dogs The vertical line at the top of each bar represents the standard error of the mean The mean myocardial Rb^{86} clearance of pulmonary-embolized dogs was greater than the corresponding control significantly in all 6 different myocardial zones ($p < 0001$ for regions 1 and 2 $p < 001$ for region 3 $p < 0001$ for region 4 and 5 and $p < 001$ for region 6)

Table II Rb^{86} clearances for different myocardial regions (as shown in Fig 1)

Regions	Rb^{86} clearance (ml /min /Gm) Mean	± S E	Number of observations
Control			
1	0 9953	0 091	10
2	1 0366	0 087	10
3	1 3746	0 065	10
4	1 2574	0 070	10
5	1 3549	0 087	10
6	1 2835	0 119	10
Pulmonary embolization			
1	1 7881	0 092	10
2	1 8072	0 066	10
3	1 9555	0 115	10
4	2 0472	0 088	10
5	2 1269	0 096	10
6	2 1 41	0 111	10

Each region represented by mean clearance ± S E 10 [illegible] In the right ventricle ([illegible]) [illegible] value of pulm emb-embolized dog (1 79 4) > [illegible] (1 047) [illegible] $p < 001$ [illegible] clearance value [illegible] (2 0472) > [illegible] (1 31 4) [illegible] $p < 001$

The foregoing discussion however would not explain the significant increase in coronary blood flow in the left ventricle when the tension time index was not increased after pulmonary embolization Gregg and associates[4] similarly observed an increase in left coronary inflow after elevation of right ventricular pressure They attributed this coronary vascular response to the extensive anatomic distribution of the ramus descendens of the left coronary artery into the right ventricle Cross[15] however postulated that a transmitter substance which relaxed left coronary vasomotor tonus is released when pressure in the right ventricle is increased Just how this coronary vascular response is mediated is beyond the sco

of the present data. Studies are now in progress concerning this problem.

Summary

The myocardial Rb[86] clearance of the different regions of the right and left ventricles was studied in the intact anesthetized dogs after pulmonary embolism. The results show that the total mean Rb[86] clearance of the right ventricle in the pulmonary embolized dogs was significantly higher than in the control dogs. Likewise, in the left ventricle the difference between the total mean Rb[86] clearance in pulmonary embolized dogs and that in the control animals was significant.

We wish to express our gratitude to Miss Avelina S. Sanchez, Messrs. Lamberto Tarayno, Rustico Vicente, and Patricio Cambay for their technical assistance in the performance of these experiments. We are also grateful to Dr. Arturo Librea and Mr. Charlemagne Tamondong of the Department of Biostatistics, Institute of Hygiene, University of the Philippines, for the statistical analysis of the data.

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Isoproterenol-induced myocardial necrosis
A histochemical and electron microscopic study

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Myocardial lesions induced by means other than vascular occlusion have been the subject of intensive study during recent years.[1] Relatively little attention has been paid to the electron microscopic and histochemical features of these types of myocardial necrosis, but the electron microscopic study of the Plasmocid lesions in skeletal muscle[2] has demonstrated dramatically the fact that what appears to be simple muscle necrosis under the light microscope can take on a much more specific meaning when examined by more sophisticated techniques.

The experimental cardiovascular necroses induced by catecholamines closely resemble those of coronary artery disease in that in the lesions in human beings catecholamines act as mediators of sympathetic effects and as agents capable of causing severe myocardial hypoxia and associated metabolic derangement if compensatory coronary dilatability is impaired.[4] Although experimental lesions have been produced only by the administration of large doses of catecholamines,[1] their clinical counterpart occurs in myocarditis resulting from prolonged infusions of norepinephrine.[5,6] Similar lesions have also been described in patients with pheochromocytomas.[1]

A number of sympathomimetic amines are capable of causing myocardial damage,[7] but the cardiotoxic action of isoproterenol, which induces infarct-like necrosis, has been of particular interest since standardized dosages consistently produce myocardial lesions of reproducible severity.[1] It was first assumed that myocardial hypoxia was the main factor in the pathogenesis of these lesions,[1] but later it became evident that the degree of myocardial damage could be modified by complex interactions between catecholamines, mineral corticoids, and electrolytes. Further experiments showed that pretreatment with either desoxycorticosterone acetate or 9-α fluorocortisol[11] or with a potassium-deficient diet[1] increased the severity of the lesions. Glucocorticoids had no protective effect,[11] but monoamine-oxidase inhibitors did provide some protection against isoproterenol-induced cardiac necrosis.[12]

Since catecholamines exert profound

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effects on lipid metabolism and since fatty change in the myocardium is a prominent feature of the catecholamine lesions[1] we combined in this study the techniques of histochemistry and electron microscopy in an effort to determine the morphologic effects of isoproterenol on the myocardium especially in regard to the relationship between lipid deposition and myocardial injury

Materials and methods

Male adult rats of the Holtzman strain were injected subcutaneously with 85 mg per kilogram of isoproterenol and killed by decapitation at intervals of 5 15 30 and 60 minutes and 2 4 6 8 12 16 24 and 48 hours A few animals were injected with 1 mg per kilogram of epinephrine and killed at similar time intervals the hearts were excised and representative tissue blocks were taken for electron microscopy The remaining tissue was frozen rapidly for cryostat sectioning Control animals (untreated) were killed at the same time and the tissues were processed simultaneously

I Histochemical techniques (1) Hematoxylin eosin for routine observation (2) Plasmal reaction for plasmalogens[14] (3) Lipid stains Sudan black B for light microscopy[15] benzpyrene caffeine[16] and phosphine 3R[17] for fluorescence microscopy Both types of fluorescent preparations were examined with a Reichert Zetopan microscope equipped with an HBO 200 mercury vapor arc lamp Primary filters Corning 5840 and Jena UG 1 were equally satisfactory when combined with a GG 9 secondary filter Fluorescence photomicrographs were taken on 35 mm high speed Ektachrome color film daylight type[18] (4) Succinic dehydrogenase[19] (5) Cytochrome oxidase[9] (6) The general morphology of the tissue was studied by phase contrast microscopy on unstained sections

II Electron microscopy Blocks measuring approximately 0 5 mm were fixed by immersion in 1 per cent phosphate buffered osmium tetroxide pH 7 4[1] for 2 hours at 1 C Dehydration was carried out in 70 per cent 95 per cent and absolute ethanol over a period of 2 hours The blocks were then embedded in a Maraglas Cardolite mixture according to the method of Freeman and Spurlock Sections were made with an LKB ultramicrotome and examined unstained with either an RCA EMU3C or Siemens Elmiskop I electron microscope

Results

The gross and routine microscopic findings in the hearts of the experimental animals were identical to those already described[1]

Histochemical observations

1 SUCCINIC DEHYDROGENASE The most striking histochemical change observed was a rapid increase in the succinic dehydrogenase activity of the mitochondria (Figs 1 3) A marked rise was already evident in the 5 minute experiments The intensity of this change was not regular throughout the tissue but was evenly distributed in individual fibers so that each one reacted as a single unit In some of the areas of increased succinic dehydrogenase activity the mitochondrial morphology differed from that of normal myocardium (Figs 3 6) The mitochondria were larger and more spherical and their formazan deposits were darker than those in the mitochondria of surrounding areas The initial rise in succinic dehydrogenase activity was followed by a gradual fall At 6 and 12 hours (Figs 5 and 6) there were areas of myocardium with markedly diminished enzymatic activity interspersed with normally reacting fibers and with fibers still retaining their increased reactivity and containing very dark spherical formazan deposits These changes progressed gradually so that at 24 and 48 hours areas of frank necrosis with very little enzyme activity were present (Fig 4) mainly at the apical portion of the left ventricle and throughout the subendocardium

2 CYTOCHROME OXIDASE In contrast to the succinic dehydrogenase reaction the cytochrome oxidase reaction remained unchanged until there was evidence of early necrosis at 6 and 12 hours At this time a decrease in enzyme activity was noted which progressed in the same manner as the succinic dehydrogenase reaction The morphology of mitochondria was less satisfactorily preserved by this technique than by the succinic dehydrogenase method

3 LIPID CHANGES Diffuse scattered deposition of very small lipid droplets occurred during the first 4 hours after the administration of isoproterenol (Fig 9) In fibers laden with lipid these droplets were distributed fairly homogeneously throughout the cytoplasm Electron microscopy confirmed the fact that the droplets

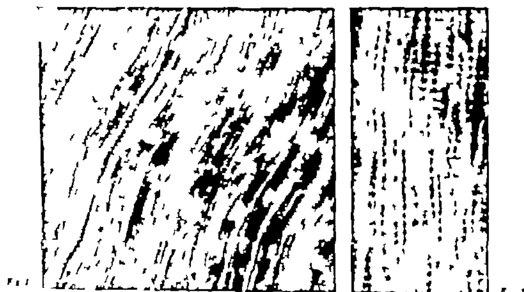


Fig 1 Normal rat heart ×100 succinic dehydrogenase reaction illustrating the normal distribution of the enzyme which is limited to the mitochondria The nuclei stand out as oval unstained areas The perinuclear zones show increased staining which is attributed to the high concentration of mitochondria at these sites

Fig 2 Rat heart ×1 500 succinic dehydrogenase reaction showing the discrete character of the mitochondrial formazan deposits The rows of mitochondria can be seen in their usual orderly arrangement



Fig 3 Rat heart 5 minutes after administration of isoproterenol ×200 succinic dehydrogenase reaction Note the change in the pattern of staining and the increase in the intensity of the reaction

were indeed lipid and not degenerating mitochondria After 4 hours the deposition of fat became more generalized and nearly all the fibers contained minute lipid droplets The fatty change was more evident in the subendocardial region than elsewhere from 8 to 10 hours after treatment zones of obvious injury which contained more lipid than adjacent areas were then present After 12 hours pale infarct like lesions were present throughout the subendocardium especially at the apex These areas (Figs 10 13) which varied from a few fibers to fairly extensive apical in



Fig 4 Rat heart 4 hours after isoproterenol ×200 succinic dehydrogenase reaction In this field most of the fibers are returning to their normal state One fiber in the center shows changes of early damage

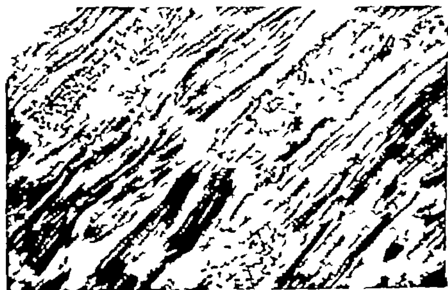


Fig 5 Rat heart 6 hours after administration of isoproterenol ×200 succinic dehydrogenase reaction demonstrating the patchy distribution of the areas of cellular damage The individuality of the histochemical reaction of each fiber can be appreciated in this view The areas corresponding to the intercalated disks are clearly visible

farcts contained large amounts of neutral fat in the form of droplets of various sizes both in the muscle fibers and in the surrounding inflammatory cells. The degree of fatty change in these areas varied from one fiber to the next (Fig 12) but large lipid droplets were present in most of the involved fibers (Figs 11 and 13) in contrast to the initial deposition of lipid when only minute lipid droplets could be detected.

The fibers which contained large lipid droplets showed a decrease in succinic dehydrogenase and cytochrome oxidase activity that was roughly proportional to the increase in neutral lipid. The plasmal reaction was less intense in these fibers than in the remainder of the myocardium.



Fig 6 Rat heart 12 hours after isoproterenol ×200 area showing one normal myocardial fiber surrounded by partially damaged fibers

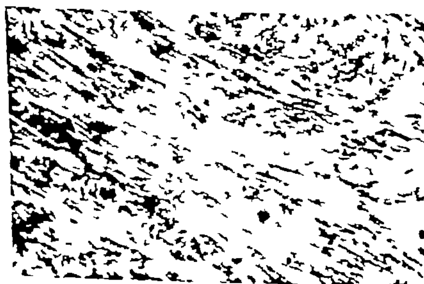


Fig 7 Rat heart 48 hours after isoproterenol ×100 Succinic dehydrogenase reaction area at the apex of the left ventricle with changes of far advanced necrosis Very little enzymatic activity remains in the cell

The mitochondria of many of the fibers that contained only small lipid droplets appeared to be essentially normal by electron microscopy and by the enzymatic techniques used here. By the same criteria, however, the presence of large lipid droplets was consistently associated with mitochondrial damage.

Sudan black B staining failed to demonstrate clearly the very small lipid droplets seen in the initial stages of lipid deposition. For this reason, fluorescence microscopy methods for lipid histochemistry were used. The superiority of these techniques over those commonly employed in light microscopy has been demonstrated elsewhere.[18]

Electron microscopy. Sections of the myocardium (Figs. 14 and 15) of the control animals showed even arrays of myofibrils separated by rows of mitochondria. Flattened vesicles of the sarcoplasmic reticulum were present between the mitochondria and in the perinuclear area. Elongated nuclei surrounded by closely packed mitochondria were occasionally encountered. Intercalated discs were prominent, consisting of closely approximated cytoplasmic membranes of adjacent cells. Desmosomes were present on the discs at varied intervals, both in the regions of myofibrils and between them. Particulate glycogen was abundant in these preparations in the form of round or stellate-shaped granules of high electron density, about 150-250 Å in diameter. Glycogen granules were especially numerous in the perinuclear areas and immediately under the cytoplasmic membrane. They were present also between and within the myofibrils.

One-half hour after the administration of isoproterenol, most of the fibers examined appeared to be essentially normal. In a few fibers there was slight swelling of some of the mitochondria. Such mitochondria were ordinarily present in all parts of a particular cell or group of cells, although immediately adjacent cells appeared to be essentially normal. The Z bands in many of the affected cells were extremely dense and appeared to be two to three times as thick as those of the normal cells (Fig. 16).

Two hours after treatment (Figs. 17 and 18) the mitochondrial changes were somewhat more pronounced than at one-half hour. Some of the affected mitochondria showed a loss of cristae beginning in one end and a replacement of these cristae with a coarsely granular substance. Vesicles which contained this granular material were occasionally encountered and were identifiable as mitochondria only by the presence of a single crista or part of a crista.

The affected areas were more numerous than at one-half hour. The sarcoplasmic reticulum throughout the entire myocardium was swollen; the ordinarily flattened vesicles were more spherical and their internal density was slightly greater than in the control animals. The amount and distribution of glycogen was unchanged.

Eight and more hours after administration, the myocardial changes were still localized in small areas, although these areas were more numerous than earlier. Almost all of the mitochondria were greatly swollen, and the cristae were diminished in number. The Z bands of some fibers had lost their high electron density, and the Z bands were poorly defined. Some fibers from the same areas were completely devoid of striations, and the myofilaments were not discernible, so that these fibers appeared to be homogeneous masses (Fig. 19). In the spaces between myofibrils lipid droplets were numerous. These droplets ranged in size from 100 mμ up to as much as 5 μ in diameter. Many of them, especially the smaller ones, were enclosed by membranes.

In the remainder of the myocardium the mitochondria and myofibrils appeared to be unaltered. The endoplasmic reticulum throughout the myocardium, however, was swollen, forming spherical vesicles between the mitochondria. The internal density of some of these vesicles was greater than in those of the control animals. Dense bodies closely resembling lipid droplets were found within a few such vesicles (Fig. 20).

Discussion

The experimental observations presented in this study are compatible with the concept that hypoxia plays a large role in the pathogenesis of these lesions. The subendocardial distribution of the myocardial necroses is certainly in strong support of

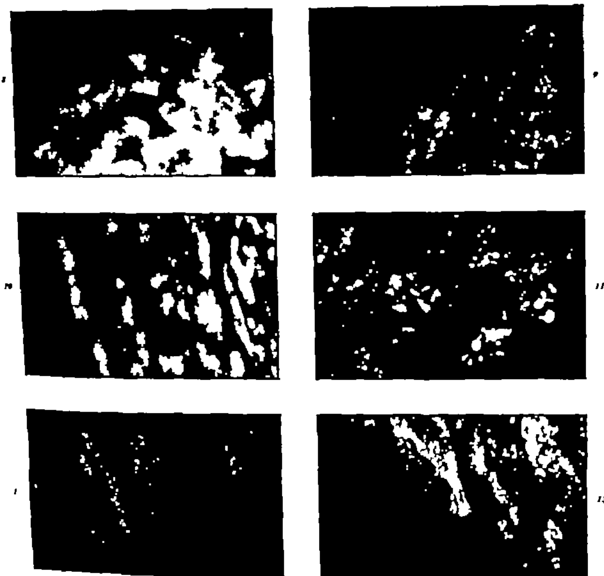


Fig. 8 Normal rat heart benzpyrene stain ×400 Cross secti of myocardial fibers how ng interfil llary sta ning which correspond t the phospholip l and other complex lip d contained the mitochondria nd in the endoplasm reticulum F t droplet re not seen in thi photograph but can be encountered sionall in few fibers in apparentl normal rat be rt

Fig. 9 Rat heart 4 hours after isoproterenol ×200 benzpyrene stain The diffuse deposition of minute lipid droplets is evident throughout

Fig. 10 Rat heart 16 hours after isoproterenol ×100 benzpyrene tain illu trat ng the mosaic like pattern of fibers inv ol ed with the deposition f l p d alternating w th relatively unaffected cell Compare w th the patterns of Fig 4 5 16

Fig. 11 Rat heart 24 hours after isoproteren l ×400 benzpy ene tain C oss sections of ubendoca d l fibers with d nced fatty change n es l nce ll y numerou l rge lipid droplet Compare w th Fig 8

Fig. 12 Rat heart 48 hours after isoproterenol ×100 phosphine stain The green fluorescence corre pond t l p d droplets in the myocardial cell Not the rel t el large ize of the l p d d oplets and the irregul r d tribution of the fatty change

Fig. 13 Rat heart 48 hours after isopr teren l ×100 be pyrene stain counter tained w th eochr Photo gr ph of the edge of inf t l ke re d onstrating the ery hea depos tion of lip d at the border zo e of ner otic t ue Cen ol l ab h w f int nge fluorescence

this idea. There is very little question that catecholamines can induce severe myocardial ischemia as the *result* of the increased demand for oxygen that they impose on the coronary circulation by their stimulatory effect on myocardial metabolism. The large doses used to produce these lesions *result* in obvious cardiac failure

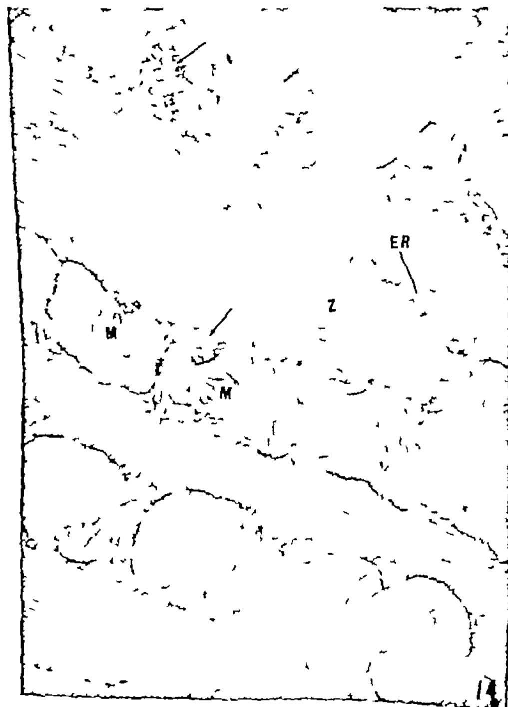


Fig. *14*. Longitudinal section of normal rat myocardium. Note the even arrangement of the mitochondria, the numerous glycogen particles (arrows) and the thin tubules of the *endoplasmic reticulum*. ×31,500. *M*, Mitochondria; *ER*, Endoplasmic reticulum; *Z*, Z bands.

It is impossible to separate completely the indirect effects of cardiac failure hypoxia and their associated metabolic derangements from a direct toxic action of isoproterenol on the myocardium but our observations[1] suggested that the lesions induced by isoproterenol may differ somewhat from those induced by other cate



Fig. 15. Slightly oblique section of normal rat myocardium. Note the thin tubules and vesicles of endoplasmic reticulum between myofibrils and the glycogen particles (*arrows*). ×31,500. A, A band; *Z*, Z band; *M*, Mitochondria; *ER*, Endoplasmic reticulum; N, Nucleus.

cholamines. Further study is necessary before any definite conclusions can be reached.

With these considerations in mind and since there are no published histochemical or electron microscopic studies of isoproterenol induced myocardial necrosis, we have compared our results with those



Fig. *16*. Longitudinal section of rat myocardium taken one half hour after the administration of isoproterenol. Note the much thickened Z bands and the clumps of glycogen (*arrows*). ×31,500. M, Mitochondria. Z, Z band.

reported in histochemical and electron microscopic studies of shock myocardial ischemia early myocardial infarction and autolysis [4,8] There are differences between these data and ours mainly in the time sequence of the various components of



Fig 17 An oblique section of rat myocardium 2 hours after the administration of isoproterenol Note especially the swollen mitochondria with decreased numbers of cristae Such grossly affected mitochondria are interspersed among essentially normal appearing mitochondria ×20 000 M Mitochondria

these changes For this reason the dif ferent elements of the myocardial lesions will be discussed separately

Changes in contractile elements The first observable change in the myofibrils was a thickening of the Z lines in fibrils of the affected areas Such thickenings closely resembled contraction bands however the sarcomere length in these fibrils was no dif ferent from that in the unaffected ones

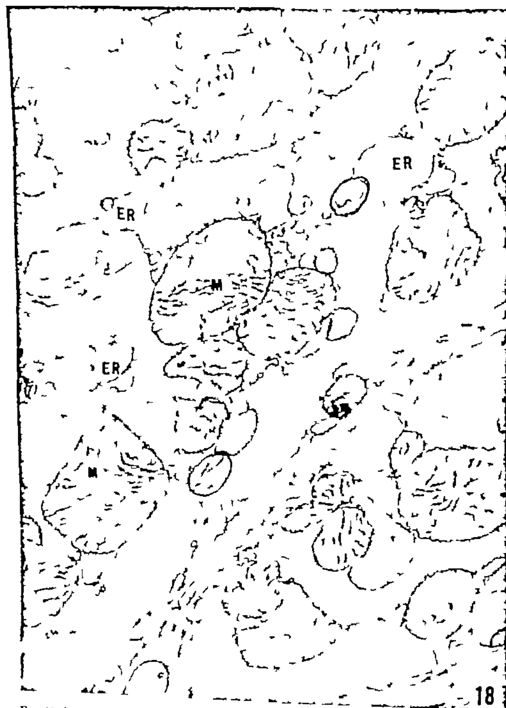


Fig 18 A section of rat myocardium 2 hours after the administration of isoproterenol Note the dilated vesicles of endoplasmic reticulum ×20 000 M Mitochondria ER Endoplasmic reticul

This was accompanied by an increase in electron density of the I band region which was marked in the early stages but became less pronounced later on

Except for these early changes in the I bands the changes observed in the myofibrils resemble closely those described in necroses caused by other means[4,8] that is,

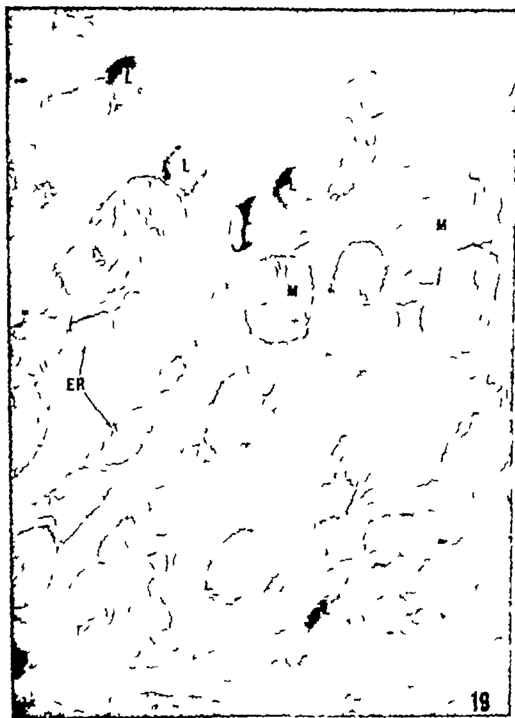


Fig 19 A slightly oblique section of rat myocardium 12 hours after the administration of isoproterenol Note the swollen mitochondria dilated endoplasmic reticulum and lack of discernible striations X20 000 L Lipid droplets ER Endoplasmic reticulum M Mitochondria

a fading of striations, loss of detail in the actin and myosin filaments and finally a melting together and fragmentation of the contractile filaments.

Glycogen changes. Glycogen granules were first described in the myocardium by Fawcett and Selby,[11] although the first report of the electron microscopic findings

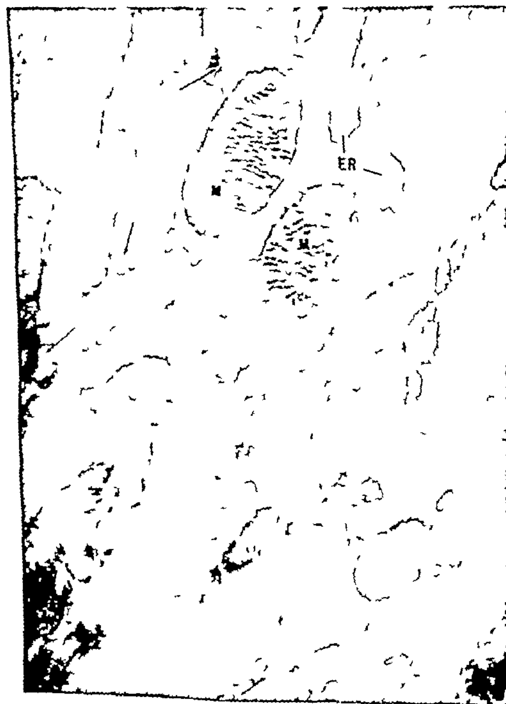


Fig. 20. A cross-section of a relatively unaffected area of myocardium 24 hours *after* the administration of isoproterenol. The mitochondria are essentially normal, but the endoplasmic reticulum dilated. Some of the nuclei contain a dark material which resembles lipid (*arrows*). ×31,500. M, Mitochondria; *ER*, Endoplasmic reticulum.

in myocardial ischemia and infarction[18] made no mention of them Previous histochemical studies by Yokoyama indicated a decrease in glycogen at 1 hour after infarction although Kaufmann and associates[9] emphasized the erratic distribution of glycogen in the myocardium The electron microscopic study of Caulfield and Klionsky[20] reported glycogen granules as being present only in the perinuclear area (this area is now known to have the highest concentration) and showed a marked glycogen reduction after 5 minutes of ischemia They observed a sharp distinction between fibers which had a marked decrease in glycogen and those which had a normal content The loss of glycogen was regarded as the earliest evidence of myocardial ischemia These data agree closely with the results obtained by chemical methods which showed a reduction in glycogen within a few minutes after coronary artery ligation[23,24]

We have demonstrated the presence of glycogen throughout the interfibrillary spaces and within the myofibrils Even with these technical refinements the changes observed in myocardial glycogen did not precede the changes in the morphology of the mitochondria or of the endoplasmic reticulum but occurred concomitantly with them over a period of hours This contrasted with the results of the epinephrine experiments in which a very marked depletion of glycogen was observed prior to other changes The significance of this difference is not known but is possibly related to a specific pharmacologic effect of these drugs since the glycogenolytic and hyperglycemic effects of the various catecholamines are quite different[22] In the rat epinephrine produces marked reductions in myocardial glycogen both in vivo[40,41] and in vitro[4,44] whereas isoproterenol in the same animal is ineffective in raising the blood sugar[40] and in causing glycogenolysis[32]

Mitochondrial changes Alterations in the fine structure of mitochondria have been the most prominent electron microscopic finding in early myocardial infarction and autolysis[1,20] This is not surprising if one considers the oxidative function of mitochondria and the fact that they are very sensitive to hypoxia

Myocardial infarction causes a rapid decrease in the succinic dehydrogenase activity of the involved fibers as shown originally by Wachstein and Meisel[4] Recent work[7] indicates that these changes are detectable as early as 90 minutes after infarction

Our observations on the alterations in the mitochondrial morphology as reflected by the succinic dehydrogenase reaction are in agreement with the report of Martin and Hackel[21] on myocardial lesions produced by experimental shock in dogs however we failed to encounter the zonal lesions described by these authors either by phase contrast microscopy in the histochemical preparations or by electron microscopy

We believe that the initial histochemical changes reflect the functional state of the myocardium indicating markedly increased mitochondrial activity resulting from the stimulatory effect of catecholamines on oxidative metabolism These changes were not accompanied by structural alterations of the mitochondria other than minimal spotty swelling This was in sharp contrast to the data reported for myocardial infarction in which mitochondrial swelling was described at 35 minutes after coronary artery occlusion[20] Mitochondrial swelling resulting from cell damage or from pharmacologic agents has been studied extensively in muscle and in other tissues[44] and we wish to emphasize the fact that it is by no means a specific effect of hypoxia It is of particular interest that hyperthyroidism and hypokalemia two conditions in which the cardiotoxicity of catecholamines is potentiated[13,47] are associated with swelling of mitochondria[41,49] whereas the perfusion of isolated hearts with epinephrine[50] results in the release of intracellular potassium

After this delayed onset of mitochondrial damage the ultrastructural alterations progressed in a manner similar to that of infarction and autolysis These changes characterized by disruption of the mitochondria were paralleled by a decrease in succinic dehydrogenase activity first to normal and then to a markedly subnormal level and finally to total absence of the enzyme We consider these changes to be evidence of tissue death since they pro

gress as described by Wachstein and Meisel[4] in myocardial infarction

The reason for the difference in time of onset of the mitochondrial changes between the lesions induced by isoproterenol and those due to coronary occlusion is not clear but we believe that it is related to the fact that in the isoproterenol treated myocardium the ischemia results from a disproportionate demand for oxygen whereas in the case of coronary occlusion the supply of oxygen is completely interrupted Therefore infarction would result in a more rapid change than myocardial necrosis without vascular occlusion

Lipid changes The fatty changes associated with ischemia and infarction have been the subject of numerous studies The demonstration of the accumulation of lipid has varied in a manner consistent with the sensitivity of the technique used Thus using Sudan III Karsner and Dwyer[ ] were unable to find fatty changes until 24 hours after coronary artery ligation Kent and Diseker[4] showed fatty change with Sudan IV and oil red O after 9 hours of infarction Wartman and associates[7] found marked accumulation of fat at the end of 6 hours of ischemia by the oil red O technique Mallory and associates[ ] noted the fact that fatty degeneration was most prominent at the periphery of the infarct and attributed this to the state of the myocardium prior to infarction

Fatty degeneration of the myocardium as a result of hypoxia without actual infarction has been reported frequently clinically as in patients with angina pectoris[ ] anemic heart disease and diphtheria[ ] and in the study of sudden deaths among German aviators during high altitude flights[ ] as well as in various kinds of experimental hypoxia[ ] and as an effect of pharmacologic agents particularly overdoses of catecholamines[ ] The deposition of triglycerides caused by infusions of norepinephrine is prevented by pretreatment with phenoxybenzamine an adrenergic blocking agent[4] The lipid mobilization induced by catecholamines depends on the activation of the lipolysis of depot triglycerides[ ] with a resulting increase in the serum level of free fatty acids The heart can extract and utilize large amounts of free fatty acids and possibly triglycerides as well[ ] The exact mechanism which governs the myocardial uptake of plasma lipids is largely unknown but available evidence indicates that it is at least partly under hormonal control[44] Once the lipids have entered the myocardial cell they can either be oxidized immediately or stored in the form of triglycerides which soon become visible in the form of lipid droplets

We believe that the small lipid droplets which accumulated in the myocardium in the early stages of isoproterenol toxicity were mainly due to the lipid mobilization which is known to follow the administration of isoproterenol[ ] The extent to which lipid mobilization alone can contribute to fatty change in myocardium is unknown and much work is needed in this area The fact that the fatty change seen initially was diffuse suggests that it was due to metabolic causes rather than to local factors selective blocking of lipid metabolizing pathways cannot be excluded as a contributory factor On the other hand we consider the fatty change seen subsequently in subendocardial foci to be hypoxic in origin

There is considerable uncertainty in regard to the specific biochemical entity responsible for the accumulation of fat in injured myocardial cells Mitochondrial damage which has been postulated as a cause appears to be a reasonable hypothesis since the oxidation of fatty acids is a mitochondrial process The coexistence of fatty change in the myocardium and mitochondrial damage has been noted by Kolin[ ] who also described the formation of formazan granules of irregular size in areas of myocardial injury with the succinic dehydrogenase technique this possibly represented mitochondrial swelling He believed that the fatty change was due to lack of oxygen and ATP

In this study the histochemical association of mitochondrial damage and fatty change although frequent was not constant As stated above although cells laden with large lipid droplets showed mitochondrial damage there were numerous small lipid droplets in cells whose mitochondria appeared to be normal by electron microscopy and by the succinic dehydrogenase reaction Similarly there

were cells with grossly damaged mitochondria and little or no lipid accumulation. Therefore, the question of the relationship of mitochondrial damage to lipid deposition in the myocardium is still partially unsettled, since it is possible that there may be an appreciable time lag between the onset of functional mitochondrial damage and the detection of morphologic evidence of it by electron microscopy or histochemistry. There are no biochemical studies which show a defect in the mitochondrial oxidation of fatty acids at the time when lipid droplets begin to accumulate in the myocardium.

Changes in endoplasmic reticulum. Swelling of the endoplasmic reticulum has been observed in cardiac[illegible] and skeletal muscle[illegible] in autolysis, ischemia, and infarction. In autolysis, changes occur more slowly than in infarction. This has been attributed to the accumulation of metabolites, to edema, and to the mechanical trauma of the heartbeat.[illegible] The swelling of the endoplasmic reticulum observed at 2 hours after injection of isoproterenol was more consistent than the mitochondrial swelling. As in the case of the mitochondria, the changes occurred more rapidly in infarction[illegible] than in the isoproterenol-induced necrosis. The varying internal density of the vesicles of the endoplasmic reticulum thought to represent more than just tissue edema and the sequence of events indicated that in myocardium the lipid droplets may be formed within the vesicles of the endoplasmic reticulum.

Studies on the chemical pathology of the endoplasmic reticulum have been summarized by Fouts[illegible] who points out that the endoplasmic reticulum can be the site of drug action, especially the smooth type of reticulum such as that of muscle. Our data indicate that the best morphologic correlate of myocardial fatty change is swelling of the endoplasmic reticulum rather than mitochondrial damage, and that the lipid droplets may be formed within the membranes of the reticulum. This suggests that some of the effects of catecholamines in the myocardium may be related intimately to metabolic reactions in the endoplasmic reticulum.

Our observations concerning the deposition of lipid within the vesicles of the endoplasmic reticulum are in accordance with the biochemical studies of George and associates[illegible] showing the presence of a lipase in heart muscle, with its greatest activity in the microsomal fraction. They believe that the high concentration of lipase in the microsomes is primarily for purposes of esterification of the free fatty acids, but that under certain conditions, such as the accumulation of triglycerides, the microsomal lipase could reverse its action and thereby release free fatty acids. These, in turn, could be oxidized by the mitochondria, which are unable to oxidize triglycerides directly.

It seems likely that lipid mobilization, mitochondrial damage, depletion of high-energy phosphates, and the endoplasmic reticulum alterations may all play contributory roles in the process of lipid accumulation in heart muscle. The relative importance of these factors cannot be evaluated from purely morphologic studies. Further clarification of this problem must await biochemical studies which relate various local and systemic metabolic processes to the deposition of lipid in myocardial cells.

Summary

Electron microscopic and histochemical alterations in heart muscle after the administration of isoproterenol are described in detail. Isoproterenol-induced myocardial necrosis develops more slowly than that resulting from coronary artery occlusion.

The first prominent electron microscopic changes are thickening of the Z lines, swelling of mitochondria, and enlargement of the vesicles of the endoplasmic reticulum. Little depletion of glycogen was observed in the early stages. Fat droplets in various stages of formation were observed within the vesicles of the endoplasmic reticulum. No fatty degeneration of the mitochondria was seen.

Histochemical studies demonstrated an early rise in the succinic dehydrogenase activity, followed by a fall. No early rise was seen with the cytochrome oxidase reaction. The accumulation of fat droplets in myocardium was studied by a sensitive fluorescence microscopy technique.

The significance of these observations and the relationship of fatty change in

the myocardium to cellular injury are discussed

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Study of hemodynamic factors which alter the sequence of the second heart sound

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The two major components of the second heart sound, A_2 and P_2, are usually ascribed to successive closure of the aortic and pulmonary valves.[1] A reversal in this order, that is, the occurrence of P_2 before A_2, is associated clinically with late closure of the aortic valve. This occurs in such pathologic conditions as severe aortic stenosis, left bundle branch block, patent ductus arteriosus, and systemic hypertension.[2-4] It was an unexpected finding, therefore, to observe that P_2 occurs before A_2 under anesthesia in a significant number of apparently normal dogs.[5] The etiology of this reversal was not immediately apparent. As a result, the study summarized here was undertaken to investigate the factors responsible for the change in the timing of the second heart sound under anesthesia. In addition, the project permitted a study of the effect of various hemodynamic alterations on the timing of the component parts of the second heart sound.

Methods

Dogs which weighed between 11 and 24 kilograms were anesthetized with intravenous sodium pentobarbital. An initial dose of 30 mg. per kilogram was utilized, and supplemental doses were given as required. The aorta was cannulated through the left common carotid artery with a rigid cannula which was positioned just distal to the aortic valves. A small thoracotomy was made in the left third or fourth intercostal space under intermittent positive pressure respiration. The pulmonary artery (PA) was cannulated with a short 10F urethral cannula through a side branch. All pressure cannulas were connected to P23AA Statham transducers. In some experiments the right ventricle (RV) was cannulated via the jugular vein. The base lines of the RV and PA pressure traces were superimposed, and the sensitivities of the traces were matched. A Peiker Bad Homberg microphone was used to pick up the heart sounds from the second intercostal space at the left sternal border, and in some experiments a ceramic crystal phonocatheter was also used to record intrapulmonary artery sounds. All sound tracings were recorded using a logarithmic filter with a band pass of 200 to 4,000 c.p.s.

After the cannulations, the thoracotomy was closed, the pneumothorax was evacuated, and the animal was allowed to breathe spontaneously for the remainder of the experiment. Complete evacuation of the pneumothorax was readily determined since it was impossible to record a smooth base line on the external phonocardiogram if

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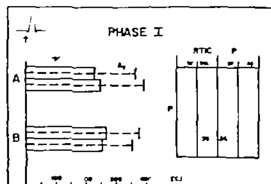


Fig. 1 Phase I data. The mean duration of the Q-A and Q-P interval is shown by the solid bars. A is the control group (A before P). Group B has the second-sound components reversed. The broken lines indicate the same data after adjustment to a standard heart rate. Aortic and pulmonary pressures are in millimeters of mercury. See text for further discussion.

residual air remained in the interpleural space.

A control 6 or 12 lead ECG was recorded from most animals in order to rule out conduction disturbances. Lead II was monitored continuously in all experiments. The Q-A and Q-P intervals were determined by measuring the time from the onset of the QRS complex in Lead II to the onset of the respective sound components in the phonocardiogram. The identity of these components was checked by comparison with the incisura of the simultaneously recorded aortic and pulmonary pressure tracings.

Respirations were monitored by recording the intratracheal pressure with a Statham differential transducer. In some experiments tracheal oxygen and carbon dioxide levels were measured with a Cambridge oxygen meter and a Harvard critical orifice carbon-dioxide analyzer.

Records were taken on a 7-channel Electronics for Medicine oscilloscopic recorder with a paper speed of 150 mm per second. Only records obtained during expiratory rest (apnea) have been analyzed; therefore respiratory variations in splitting of the second heart sound are not included in this study. Intervals of the cardiac cycle were measured to the nearest 0.003 second. Statistical significance refers to a probability level of 0.05 or less using the Student t test.

To minimize errors in the Q-A and Q-P_2 interval due to changes in heart rate, only data from beats which had similar cycle lengths were compared. In one case this was not possible. Therefore the Q-A and Q-P_2 intervals in both groups were adjusted so that they represented intervals from a cardiac cycle of 1 second. The following modification of Bazett's formulas was used[7]:

$$\text{Adjusted interval} = \frac{\text{Measured interval}}{\sqrt{\text{Cycle length}}}$$

Results

The results of this study can be divided into three separate phases. Data in Phase I were obtained from 18 experiments after repair of the thoracotomy. Phase II consists of data from 7 experiments in which pulmonary hypertension was produced by multiple small pulmonary emboli. The emboli consisted of microspheres, air, or autogenous blood clots which were injected into the PA cannula. Phase III is composed of data from 9 experiments in which acute hypoxia and/or hypercapnea was used to stress the cardiovascular system. Each phase will be presented separately.

Phase I. In 5 of 18 experiments the usual order of A_2 before P was reversed. The mean Q-A_2 and Q-P_2 intervals for the normal and the reversed groups before and after adjustment for the difference in heart rate are shown in Fig. 1. The mean A-P interval for the 13 experiments in which the normal sequence occurred was 20 msec, whereas in the 5 experiments in which reversal occurred the mean P-A interval was 11 msec. Comparison of these raw data indicates that the reversed order occurred because of a longer Q-A interval. However study of the data after adjustment for the heart rate indicates that reversal is due to both prolongation of the Q-A interval and abbreviation of the Q-P_2 time.

Prolongation of the Q-A interval should affect the pattern of left ventricular ejection. Therefore it is of interest to examine the contour of the aortic pressure pulse in the two groups. Representative records from 2 experiments are shown in Fig. 2.

Record *A* shows the normal aortic pressure contour with a rapid rise in pressure to a mid-systolic peak and a sharp drop to the incisura. However, in record *B*, where P_2 occurs before A_2, the rise in aortic pressure is slower, the peak pressure occurs later in systole, and the drop to the incisura is less. This contour is typical of the aortic pressure pulse when the sequence of the second heart sound components is reversed during anesthesia.

The average rate of rise in left ventricular pressure was approximated by assuming a left ventricular diastolic pressure of zero and dividing the time interval between the onset of the first heart sound and the beginning of the rise in aortic pressure (period of isometric contraction) into the aortic diastolic pressure. This rate was significantly lower when P_2 preceded A_2. The average rate was 3,669 mm. Hg per second for the normal experiments and 2,069 mm. Hg per second in the experiments with P_2 before A_2.

The average pulmonary arterial diastolic pressure was significantly elevated in the experiments in which P_2 preceded A_2. No significant change occurred in pulmonary systolic or systemic diastolic pressure. These values are summarized in Fig. 1.

Phase II. The presence of an elevated pulmonary diastolic pressure in the group with P_2 before A_2 suggested that perhaps these animals had an increased pulmonary vascular resistance. This was investigated by observing the effect on the second heart sound when pulmonary resistance was increased by pulmonary embolization in 13 animals with the normal sequence of A_2 before P_2. This procedure caused the components to reverse in 11, or 85 per cent, of the group.

Data from the 7 experiments in this phase in which right ventricular pressure was measured are summarized in Fig. 3. Only cycle lengths of 400 to 550 msec. were analyzed; therefore, it was not necessary to adjust these data for differences in heart rate.

It is of interest that embolization did not cause the mean aortic pressure or the Q-A_2 interval to change significantly. As a result, modification in the sequence of the second heart sound was due entirely to changes in timing of the Q-P_2 interval. In these animals, pulmonary pressure was significantly higher, whereas right ventricular diastolic (RVD) pressure remained the same. The duration of RV isometric contraction was essentially unchanged from that of the group with normal second sounds. Therefore, abbreviation of the Q-P_2 interval is due to a shorter period of RV ejection.

In 3 of the 7 animals, continued embolization was associated with a rise in RVD

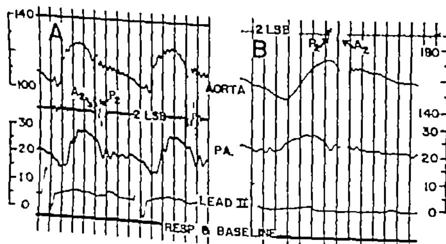


Fig. 2. A series of records showing (*A*) the normal sequence of A_2 before P_2 and (*B*) a reversed split with P_2 before A_2. Calibration is in millimeters of mercury. Time lines indicate 0.04 sec. Both sound records were made in the second left intercostal space at the sternal border.

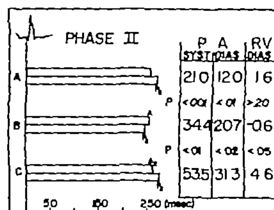


Fig. 3. Phase II data. The mean durations of the Q-A and Q-P interval are shown by the solid bars. A is the control group. B is after mild pulmonary embolization with P before A, and C is after further embolization with return of A before P. Pulmonary and right ventricular pressure is in millimeters of mercury.

pressure as well as PA pressure (Fig. 3 C). As a result of these changes right ventricular ejection was prolonged and the order of the second sound was reversed so that P_2 again followed A.

This analysis suggests that the placement of the P component of the second heart sound is affected by both the pulmonary arterial diastolic pressure and the RVD pressure. This relationship is shown in Fig. 4 in which the Q-P_2 intervals from these experiments are plotted against the PA diastolic pressure for three ranges of RVD pressure. At any given level of RVD pressure an increase in PA diastolic pressure results in an abbreviation of the Q-P interval. However, an increase in RVD pressure without change in PA diastolic pressure causes the Q-P interval to be prolonged.

The dynamic changes in right ventricular performance responsible for the relationship between the Q-P time, PA diastolic pressure, and RVD pressure are illustrated in Fig. 5. This shows two sets of tracings, each with a control pressure pulse and a superimposed postembolization pressure pulse of equal cycle length from the same animal. When emboli were injected into the pulmonary circulation the PA pressure increased in both sets of curves. In Fig. 5A there was no change in RVD pressure after embolization and both the isometric contraction and right ventricular ejection times were abbreviated. In Fig. 5B RVD pressure increased after embolization and isometric contraction and right ventricular ejection times were lengthened.

Phase III. Pulmonary embolization altered the Q-P_2 interval; however, it did not significantly affect left ventricular events. Therefore an increase in pulmonary resistance could not be the sole factor responsible for the reversal in the timing of the second heart sound which was observed in Phase I. However, the elevated PA pressure seen in these animals might have resulted from mild hypoxia secondary to the anesthesia. This was investigated by varying the CO_2 and O_2 content of expired gas and noting the effect on the second heart sound.

No significant alterations in the timing of the second heart sound occurred when inspired CO_2 was elevated to a concentration of as much as 10 per cent. However, when the O_2 concentration was reduced to an average level of 11.8 per cent (CO_2 averaged 3.4 per cent in these experiments) the sequence of the components of the

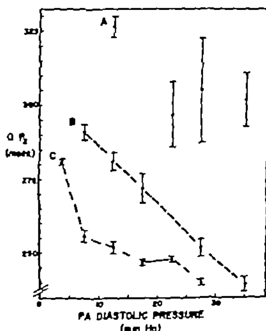


Fig. 4. Plot of the Q-P interval against the pulmonary diastolic pressure at three levels of right ventricular diastolic pressure. A, -4 to 1 mm Hg. B, 0 to 3 mm Hg. C, greater than 3 mm Hg. The vertical lines equal ± 1 standard error.

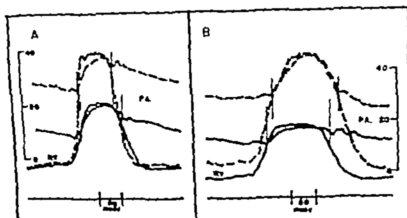


Fig. 5. Tracings of control (*solid lines*) and postembolization (*dashed lines*) right ventricular and pulmonary artery pulses of equal cycle lengths from the same animal. Pulses were aligned by superimposing the QRS complex of the electrocardiogram (*not shown*) and the base line. *A*, No postembolization change in right ventricular diastolic pressure. *B*, Increased postembolization right ventricular diastolic pressure. Calibration in millimeters of mercury.

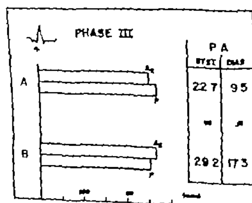


Fig. 6. Phase III data. The mean duration of the Q-A and Q-P interval is shown by the solid bars. Group *A* is the control. Group *B* shows P_2 before A. Pulmonary pressure is in millimeters of mercury. See text for discussion.

second heart sound reversed in 3 of 7 animals. The average Q-A_2 and Q-P intervals for these 3 animals are summarized in Fig. 6. It was not necessary to correct for heart rate in this series since the difference between the rate in the group that showed reversal and that in the remainder of the animals was not statistically significant.

When P occurred before A, PA diastolic pressure was higher, right ventricular ejection time was reduced, and left ventricular ejection time was prolonged as compared to the control group. These changes were all statistically significant. The reversal in these animals therefore occurred as the result of a longer Q-A_2 interval and shortening of the Q-P_2 time.

It is interesting that these 3 animals showed the same changes in the form of the aortic pressure pulse that were associated in Phase I with a reversed split of the second heart sound.

Discussion

The results of this study are in agreement with the current clinical practice of equating the timing and sequence of the second heart sound to closure of the aortic and pulmonary valves.[1] The major factor in these experiments that caused the usual sequence of A before P to be modified was a differential variation in the duration and vigor of right and left ventricular ejection.

The duration of ventricular ejection is dependent on a number of factors. Wiggers,[9] Braunwald and associates,[8] Sarnoff and co-workers,[10] and others[11] have shown that a moderate increase in vascular resistance will result in a more rapid ventricular ejection without significant change in end-diastolic pressure, stroke volume, or myocardial segment length. On the other hand, a decrease in myocardial contractility is accompanied by a decreased rate of ventricular emptying, prolongation

of ejection time and elevation of end-diastolic pressure.[11] The data presented in this communication support this concept. A mild increase in pulmonary resistance sufficient to elevate PA pressure without causing a change in RVD pressure produced reverse splitting of the second sound due to shortening of the Q-P interval. However, when pulmonary resistance was increased to the point at which it interfered with right ventricular emptying, as indicated by an increase in RVD pressure, the duration of right ventricular ejection was prolonged. The longer duration of Q-P then caused the normal sequence of the second sound to be re-established with A occurring before P.

Anoxia produced reverse splitting in 3 of 7 animals by movement of both the P and A_2 components of the second heart sound. In this situation, prolongation of the Q-A_2 interval was apparently related to a decrease in left ventricular contractility and elevation of left ventricular diastolic (LVD) pressure. Shortening of the Q-P interval could be related to a mild increase in pulmonary resistance and elevation of PA diastolic pressure without a significant change in RVD pressure.[1]

A possible explanation for the reversal of the components of the second heart sound in the anesthetized dog is suggested by the present study. That is, that a loss of left ventricular contractility, such as might occur with excessive anesthesia and/or unrecognized anoxia, combined with a mild increase in pulmonary resistance will cause alterations in ventricular dynamics of the type that lead to an abnormal second heart sound. In view of these findings, it appears reasonable to assume that a reversed split of the second heart sound under anesthesia in the dog is indicative of abnormal cardiodynamics.

Summary

In 5 of 18 anesthetized dogs the normal order of the components of the second heart sound was reversed. This reversal was due to a longer Q-A interval and a shorter Q-P_2 time. The aortic pressure pulse in these animals showed a slower than normal rise in pressure, a later peak pressure, and a smaller drop to the incisura. The pulmonary diastolic pressure was significantly higher in the group with reversed splitting.

Pulmonary embolization caused the sequence of the components of the second heart sound to reverse in 11 of 13 experiments. This occurred because of abbreviation of right ventricular ejection and movement of the P component. The data suggest that the timing of P_2 is related to the level of pulmonary arterial diastolic pressure and the right ventricular diastolic pressure. An increase in PA diastolic pressure causes shortening of the Q-P_2 interval, whereas an increase in RVD pressure without a change in PA diastolic pressure causes the Q-P interval to increase. Further embolization resulted in re-establishment of the normal sequence of A before P_2. This was accompanied by elevation of RVD pressure and prolongation of right ventricular ejection.

Anoxia due to breathing 11.8 per cent oxygen caused the second heart sound to reverse in 3 of 7 animals. The reversal was due to a shorter right ventricular ejection time and a longer period of left ventricular ejection; this caused movement of both the P and A components of the second heart sound.

These data support the concept that the timing of the second heart sound is dependent on the differential rate and duration of right and left ventricular ejection. A mild increase in output resistance causes the duration of ventricular ejection to shorten, whereas an increase in end-diastolic pressure results in a longer ejection period.

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ECG changes after cerebral stimulation

I Anomalous atrioventricular excitation elicited by electrical stimulation of the mesencephalic reticular formation

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More than 30 years have elapsed since Wolff, Parkinson and White[1] in their classic paper described an aberrant cardiac rhythm which now bears their name. This abnormal complex (WPW) is characterized by a shortened P-R interval with a concomitant widened QRS complex.

An aberrant rhythm which resembles the phenomenon observed in clinical medicine has since been produced experimentally in animals by several investigators. Weinberg and Fuster[2] reported that electrical stimulation of the posterior hypothalamus elicited cardiac arrhythmias which resembled the WPW complex. Parker, Gunn and Lynn[3] also described aberrant cardiac arrhythmias similar to the WPW phenomenon after electrical stimulation of both the posterior hypothalamus and the midbrain reticular formation.

Other investigators, including Ueda[4] and Attar, Gutierrez, Bellet and Ravens,[5] have elicited cardiac arrhythmias from electrical stimulation of these same areas, but they did not report aberrant complexes resembling the WPW phenomenon.

Furthermore, a controversy seems to have arisen as to which division of the autonomic nervous system mediates these cardiac arrhythmias. Weinberg and Fuster[2] argued for exclusive sympathetic influence, whereas Parker[3] and his colleagues ascribed the induced arrhythmias to reflex vagal control.

In an attempt to resolve the controversy engendered by these contradictory results, a series of studies was begun in this laboratory to delineate the neural structures involved in the central nervous system and to ascertain the role played by both divisions of the autonomic nervous system in the experimental production of aberrant cardiac rhythms resembling the WPW complex.

Methods

Twenty adult boxer dogs which ranged in weight between 21 and 25 kilograms were used in this study. All animals were anesthetized with thiamylal sodium* administered intravenously. The initial dosage was 10 mg. per kilogram of body weight and anesthesia was sustained with increments of 2 mg. approximately every hour

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*Surital, Parke, Davis & Company, Detroit, Mich.

The stimulating electrode made from 0.35 inch stainless steel wire and insulated with Tygon except for 1 mm at the tip was lowered into the mesencephalic reticular formation at the level of the pons. The stereotaxic coordinates used (anterior 6 mm from the interaural line, lateral 3.5 mm from the midline, depth 7.0 mm) were based upon prior empirical studies. The reference was clipped to the ear bar of the stereotaxic instrument and the stimuli consisted of 10 second trains of sine wave pulses at 60 c.p.s. The intensity of the stimulus was dictated by the threshold response of the animal and varied from 0.5 to 1 volt.

In all experiments the electrocardiogram was recorded from Standard Lead II and systemic blood pressure was measured with a Statham P23Dc transducer from a catheter inserted into the femoral artery. All recordings were made on a Grass Model 5 six-channel direct ink writing polygraph.

In 5 animals electrical stimulation of the mesencephalic reticular formation was delivered before and after bilateral section of the vagosympathetic trunks in the neck. In these subjects the distal cut ends of the nerve trunks were also stimulated.

In 5 animals the brain loci were stimulated before and after section of the spinal cord at the level of the second cervical vertebra.

In 2 animals the distal cut-end of the right vagosympathetic trunk was stimulated after cardiac arrhythmias had been previously elicited by electrical stimulation of the mesencephalic reticular formation. In these animals the left vagosympathetic trunk was intact.

Each experiment lasted about 6 hours during which each cerebral locus was stimulated several times. At the end of the experiment the animal was perfused with a 10 per cent solution of neutral formalin and the brain was removed for histologic verification of the placement of the electrodes.

Results

In all 20 animals used in this study, electrical stimulation within 2 mm in any direction of the given coordinates elicited alternate ECG complexes which were characterized by a shortened P-R interval, a widened QRS complex, constant P-P and R-R intervals, the presence of a delta wave, and a P-S interval identical to that seen in the normal complex. These arrhythmias which resembled the WPW phenomenon are illustrated in Fig. 1.

It will be noted that the anomalous atrioventricular excitation meets the criteria outlined by Hecht[8] and his colleagues for this phenomenon. These WPW-like complexes occurred with a latency of 20 to 30 seconds and persisted for 80 to 120

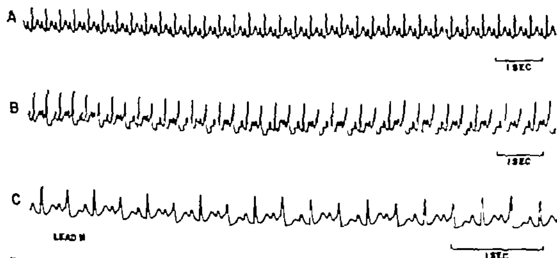


Fig. 1. Anomalous atrioventricular excitation produced by electrical stimulation of the mesencephalic reticular formation. A, Control record. B and C, Aberrant complexes at paper speed of 25 and 50 mm. per second, respectively.

seconds. The onset of these aberrant complexes was invariably preceded by an increased rate: bursts of ventricular tachycardia, multifocal ventricular premature beats, premature nodal beats, shifting atrial pacemaker, and atrial fibrillation. These bursts appeared from 8 to 12 seconds after the onset of stimulation. Sinus pauses and ventricular and nodal escape beats were in evidence in some records.

In many experiments the aberrant rhythms showed a gradual progressive lengthening of the P-R interval and a concomitant shortening of the QRS duration with eventual reversal to a normal sinus rhythm. Stimulation of the mesencephalic reticular formation consistently elicited a pronounced pressor response. The atrial, nodal, and ventricular arrhythmias coincided with the rising phase of the blood pressure and the peak of the pressor effect. The onset of the alternating aberrant complexes, however, was most frequently observed as the blood pressure was returning to its prestimulation level, and in some instances the phenomenon persisted for *several minutes after the blood pressure* had returned to its control level.

In the 5 animals in which the vagosympathetic trunks had been severed in the neck, electrical stimulation in the mesencephalon gave arrhythmic responses identical to those obtained in the intact animal. Stimulation of the distal cut ends of the vagosympathetic trunks, however, elicited variable responses. On the one hand, left vagosympathetic stimulation always resulted in bradycardia with decreased blood pressure, and in one instance this was followed by a short period of poststimulatory complete A-V dissociation. On the other hand, stimulation of the distal cut end of the right trunk evoked bradycardia with hypotension during stimulation and in one instance a brief run of atrial fibrillation. *No other arrhythmias* occurred, and the WPW-like complex was not observed in any of these 5 experiments.

In the 5 animals in which the spinal cord was sectioned after the aberrant rhythm had been elicited, further stimulation of the reticular loci failed to produce the arrhythmias.

After section of the right vagosympathetic trunk in 2 animals, electrical stimulation of the mesencephalic reticular formation elicited the aberrant WPW-like complexes. This response was subsequently abolished by stimulation of the distal end of the severed nerve trunk, which produced depression of the sinoatrial node and ventricular asystole.

Discussion

The results of this study demonstrate that an aberrant cardiac rhythm which bears a striking similarity to the WPW complex observed in clinical medicine can be produced experimentally in normal healthy dogs by electrical stimulation of the mesencephalic reticular formation. These results also demonstrate rather convincingly that the abnormal rhythm observed in this study is not a parasympathetic manifestation, but that it appears to be mediated exclusively by the sympathetic division of the autonomic nervous system, since this abnormal complex could be elicited by electrical stimulation of loci in the mesencephalic reticular formation after bilateral section of the vagosympathetic trunks. *Furthermore, the phenomenon could not be produced by stimulation of the distal cut ends of the vagosympathetic trunks, nor could it be produced after the spinal cord had been severed at the second cervical level.* These results contradict the possibility of parasympathetic participation in the aberrant complex reported in this study.

It will be recalled that electrical stimulation of the distal cut end of the right vagosympathetic trunk (left trunk intact) after the aberrant rhythm had been produced by cerebral stimulation depressed the sinoatrial node and abolished the WPW-like phenomenon. After offset of stimulation of the vagosympathetic trunk, a normal sinus rhythm was re-established, and after a short latency the abnormal ventricular complexes reappeared. Although it is impossible to differentiate with absolute certainty between ventricular pre-excitation and fused ventricular premature beats when the abnormal electrocardiographic complex is alternating with a normal sinus beat, the present results do show that it is unlikely that the ventricular response is the result of an independent ectopic focus, but is dependent

upon the impulse originating from the sinoatrial node It might be pointed out that the anomalous complexes although they resemble the WPW phenomenon observed clinically may be mediated by entirely different mechanisms However much work is needed to elucidate the extracardiac and intracardiac mechanism responsible for this conduction abnormality

Many investigators including Wang and Ranson[7] and Alexander[8] have shown that pressor responses can be elicited by electrical stimulation in the mesencephalic reticular formation And although the present results show that the loci stimulated play what might prove to be an extremely important role in cerebral organization and regulation of cardiovascular function it would be futile to speculate upon the precise role of this neural region until additional anatomic and physiologic data are available This point has been strongly emphasized by Brodal[9] in his recent monograph on the brain stem reticular formation

Summary

Unipolar electrodes were stereotaxically implanted in the mesencephalic reticular formation of adult boxer dogs anesthetized with Surital sodium Electrical stimulation (60 c p s of alternating current) of a circumscribed area at the level of the pons produced an anomalous atrioventricular excitation similar to the WPW phenomenon observed in clinical medicine Bilateral section of the vagosympathetic trunks had no effect on the production of this aberrant cardiac rhythm however it could no longer be elicited after section of the spinal cord at the level of the second cervical vertebra These results demonstrate that the WPW like complexes observed in this study are mediated exclusively by the sympathetic division of the autonomic nervous system Electrical stimulation of the distal cut-end of the right vagosympathetic trunk after the aberrant rhythm had been elicited by cerebral stimulation abolished the abnormal response

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The relative amounts of DNA and concentrations of RNA in heart muscle of normal and hypertrophied hearts

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When the human heart has a variety of increased workloads imposed upon it by disease, it undergoes an increase in weight and an increase in the thickness of the ventricle which assumes the burden of the added load. The question whether this increase in weight and size is the result of increased DNA or RNA synthesis in the myocardial cell or is exogenous to the heart muscle cell has not been resolved, although some evidence has been advanced that cardiac hypertrophy is under the control of cardiac muscle cytoplasm.[1] Some have ascribed cardiac hypertrophy to cellular hypertrophy alone,[2] and others have believed that cellular hypertrophy in connection with possible hyperplasia of myocardial cells is responsible for over-all cardiac hypertrophy.[3,4] This paper is an attempt to resolve some of these questions.

Materials and methods

In a series of 100 normal and hypertrophied human hearts, pieces of tissue were removed from the left ventricular wall, interventricular septum, right ventricular wall, and right and left atrial muscle. Hearts which weighed less than 400 grams and had a left ventricular wall that was 15 mm. or less in thickness and a right ventricular wall that was 3 to 5 mm. in thickness were considered to be normal for this study. Those hearts which exceeded 400 grams in weight and had a left ventricular wall that was greater than 15 mm. in thickness or a right ventricular wall that was 5 mm. or more in thickness were considered to be hypertrophied. The tissues were fixed in buffered formalin, pH 7.12-7.14, for 1 week, and then dehydrated in a step series of alcohols, cleared in chloroform, blocked in paraffin, and sectioned at 4 micron thickness. The sections were stained by the Feulgen technique after 10 minutes of hydrolysis in N HCl. No counterstain was applied. The methyl green-pyronine staining method was used in the study of RNA content of the same tissues. All suitable sections were studied by standard microspectrophotometry.[5,6]

A monochromatic light 546 mμ was passed from a Bausch and Lomb grating monochromator through the Feulgen-stained sections in a Bausch and Lomb zoom microscope with standard optics. The amount of light absorbed by the Feulgen-stained nuclei was measured by a Photovolt multiplier set at range 1

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Table I Correlation coefficients for DNA in hearts

	TLV	IVS	RV	RA	LA
TLV	1	4997	5232	5307	2428
IVS		1	6474	5018	4735
RV			1	3997	4707
RA				1	2753
LA					1

Correlation [illegible] DNA [illegible] different areas of the [illegible] normal heart. TLV [illegible] part of left ventricle IVS [illegible] RV Right [illegible]

Table II Correlation coefficients for DNA in hearts of 400 Gm or heavier

	TLV	IVS	RV	RA	LA
TLV	1	7667	1469	2207	4674
IVS		1	1559	0632	0664
RV			1	4382	3649
RA				1	5257
LA					1

The correlation [illegible] DNA [illegible] heavy hearts (400 Gm [illegible])

attached to the ocular end of the microscope tube and the field measured was restricted to that of slightly larger than one heart muscle nucleus by a diaphragm inserted in the optical path Sections were moved about at random so that many nuclei passed across this restricted field and the nuclear peaks or absorptions of light of each nucleus were recorded on a Brown Honeywell recorder wired to the Photovolt multiplier

The contribution of endothelial cell and inflammatory cell DNA to the recordings was minimized by constant visualization of the tissue through the binocular portion of the two way optical system and restriction of the scanned fields to cardiac muscle

In the study of RNA content of the tissues by the methyl green pyronine method the monochromatic light was in the blue green spectrum at 500 mμ in order to minimize nuclear effects and the sensitivity of the Photovolt multiplier was set at range 10 insufficient to record nuclear absorption but adequate for registering RNA in the cells

The relative total amounts of DNA per nucleus were obtained from measurement of the amplitude of the nuclear peaks on the graphs and those tracings with the most nuclear hits were used in the computations Thus a series of 26 normal hearts which weighed under 400 grams[7] were used and a corresponding number of hearts which were over this weight were available for comparison Comparisons of normal hearts with those hearts which had a right ventricular wall thickness of over 5 mm and those hearts which had a left ventricular wall thickness of over 15 mm were also made No attempt was made to measure the absolute DNA content per nucleus in either normal weight or hypertrophied hearts Since the plug areas in the DNA study covered single nuclei it follows that the relative total amount of DNA in nuclei were obtained the plug area in the RNA study did not cover the entire cell and therefore RNA concentrations per cell were measured

Results and comments

The data accumulated from the study of the normal hearts were analyzed statistically and the relative DNA contents per nucleus of the septum right ventricular wall and left ventricular myocardium were correlated with one another (Table I) The values in this first correlation indicate that the nuclear DNA is fairly constant from area to area in the ventricles The range in the positive correlations is an indication of experimental error such as variation in section thickness and occasional measurement of a nucleus bearing a Feulgen negative nucleolus[8]

The DNA content per nucleus in the left ventricle in a series of 20 hearts of normal weight was compared with that in the same area of a group of 28 hypertrophied hearts and no significant difference was found

The variation in DNA per nucleus in various areas of the hypertrophied heart (Table II) could be explained on the basis of increased RNA synthesis in each with resultantly greater nucleolar activity and Feulgen negativity This would vary over as wide a range as the degree of hypertrophy with considerable scatter expected

Table III Mean RNA concentrations of normal and hypertrophied hearts with corresponding standard deviations (S D) and number (n) in each sample

	Normal hearts					Hypertrophied hearts				
	TLV	*IVS*	*RV*	*LA*	*RA*	*TLV*	*IVS*	*RV*	*LA*	*RA*
Mean	67 20	60 17	59 09	54 75	54 21	95 53	95 33	91 29	77 33	79 69
S D	26 89	28 72	23 02	26 78	22 38	13 63	17 78	24 14	16 47	18 74
n	25	23	22	20	19	15	15	17	15	16

Table IV RNA correlation coefficients for different areas of normal heart

	TLV	*IVS*	*RV*	*RA*	*LA*
TLV	1	909	668	331	855
IVS	909	1	793	515	861
RV	793	793	1	239	667
RA	331	515	239	1	486
LA	855	861	667	486	1

Occasional high peaks were found in the DNA runs in an approximate ratio of 3 28 or 1 9 These were interpreted as representing possible ploidy in cardiac cells or as representing beat leading cells[8] Purkinje or nodal type cells In 3 hearts which had a left ventricular wall total nuclear count of 67 9 such peaks were found in 13 4 per cent A group of 5 hearts which ranged in weight from 400 to 540 grams had a total of 8 peaks out of a total of 47 nuclei counted or 17 5 per cent Since these peaks were sharp and free of splits it seems reasonable to assume that they represent the effects of nuclear ploidy Furthermore the peaks were nearly always roughly double the average nuclear value for relative DNA

In this same two series when the average relative DNA per nucleus was computed from inclusion of all peaks it was found that there was on inspection no apparently significant difference between hearts of normal weight and hypertrophied hearts

The study of the sections treated with methyl green pyronine disclosed that in the normal heart the RNA concentration in the various ventricular areas is somewhat variable tending to be highest in the left ventricle and considerably less in the heart muscle cells of the two atria with less in the right atrial muscle than in the left These values could well be related to differences in load or chamber pressure from area to area as noted by several workers[1, 11] and the RNA concentration per cell is in direct proportion to the amount of work imposed per area as measured by pressure loading of the four heart chambers The RNA concentrations and correlation coefficients found are shown in Tables III and IV

In a series of 15 hypertrophied hearts serially selected the left ventricular concentration of RNA was compared with that in 25 hearts which weighed less than 400 grams It was found that the RNA concentration in the hypertrophied hearts was significantly higher than that in the control group (t = 3 785 significance p < 01) The values for RNA (arbitrary units) concentration in normal and hypertrophied hearts are shown in Table III

The RNA concentration correlation coefficient of left ventricle versus interventricular septum was 909 and significantly different from that of left ventricle versus right atrium (p < 05) The IVS LA coefficient was also significantly different from the RV RA coefficient p < 01 the IVS LA correlation was significantly different from the RLV RA correlation p < 05 TLV IVS versus RA RV was also significantly different p = 01 All correlations are shown in Table V

The correlation coefficients for RNA concentration in various areas of hypertrophied hearts are less close than those for normal hearts which suggests unequal loadings in various chambers and a variation in

response to this stimulus since those hearts with left ventricular hypertrophy alone and those with both left and right ventricular hypertrophy were not separated in this phase of the study The noncorrelation of TLV LA suggests that the RNA concentration increases markedly in the left ventricular wall as compared to that in the left atrial wall and that the left atrium does not participate so greatly in the hypertrophy process as does the left ventricular muscle

A similar comparison of RNA concentration in hypertrophied right ventricles with that in right ventricles of normal thickness could not be evaluated because of the scarcity of hearts with pronounced right ventricular hypertrophy

Koplitz and Priest[14] have experimentally produced hypertrophy in the hearts of adrenalectomized male rats subjected to arterial hypertension induced by salt loading plus the administration of desoxycorticosterone and have found an increase in cardiac DNA of 20 per cent in these animals RNA was also found to be increased

*Table V Correlation coefficients of different paired areas versus other pairs**

TLV–IVS	[illegible]	TLV–RV	p < 05
TLV IVS	[illegible]	TLV–RA	p < 01
TLV–IVS	[illegible]	IVS–RA	p < 05
TLV–IVS	[illegible]	RV–RA	p < 01
TLV IVS	[illegible]	RA–LA	p < 05
TLV–RA	[illegible]	TLV–LA	p < 05
TLV–RA	[illegible]	IVS–LA	p < 05
TLV–LA	[illegible]	RV–RA	p < 05
IVS–RV	[illegible]	RV–RA	p < 05
IVS–LA	[illegible]	RV–RA	p < 01

*[illegible] RNA [illegible]

Table VI Correlation coefficients RNA concentrations in hypertophied hearts

	TLV	IVS	RV	LA	RA
TLV	1	39	43	– 02	38
IVS		1	72	47	20
RV			1	43	43
LA				1	29
RA					1

by 29 per cent in their study An increase in cardiac weight of 19 per cent was considered to be significant The data were interpreted as an increase in numbers of cardiac nuclei with cardiac enlargement as the best explanation for the changes found Since tritiated thymidine uptake was found in both normal and hypertrophied hearts it is evident that in both there was DNA synthesis

Norman and Carter[3] produced anemic cardiac hypertrophy in rats on a diet that was deficient in copper and iron They found a significant increase in the weight of the hearts of those rats as compared to the hearts of control rats RNA concentration was found to be also significantly increased in animals which were given neither copper nor iron and in those animals which received both copper and iron RNA concentration was increased significantly in those animals which received neither iron nor copper and in those given copper only DNA concentration was significantly increased in none but DNA per heart was elevated significantly in animals which received no dietary supplement and copper alone The elevation of the RNA/DNA ratio was interpreted as indicating a predominance of cellular hypertrophy in the subject rat hearts However since DNA duplication is necessary for and is ordinarily followed by cell division the possibility of cell division also seemed to be reasonable to those workers The increase in DNA could also be explained by ploidy or by proliferation of blood vessels

In studies similar to those of Norman and Carter[3] Sumner and McIntosh found a significantly increased mean heart weight decreased DNA concentration increased RNA/DNA and increased total RNA and protein content in the hearts of anemic rats when these were compared with the hearts of control rats Furthermore they found no statistically significant changes in the RNA concentration or total DNA content of the subject hearts in the anemic rat group They believed that the predominant cellular change in the rats with heart enlargement due to dietary deficiency was an increase in myocardial cell size

The over all data obtained in this study suggest that the control of cardiac hypertrophy is within the myocardial cell cyto

plasm and as would be expected is mediated through the RNA fraction since it controls protein synthesis It would appear that although there may be some increase in DNA synthesis in the heavy heart the synthesis is likely rapid and there is a turnover into increased RNA replication

An experiment utilizing fragmentation of cardiac muscle cells and separation of normal and possible polyploid nuclei by differential centrifugation followed by DNA analysis chemically and in connection with nuclear size distribution data obtained electronically would resolve some of the mystery surrounding the role of DNA in hypertrophy

Summary

The relative amount of DNA in heart muscle nuclei was studied by Feulgen microspectrophotometry in normal and hypertrophied hearts and there was found to be no significant quantitative difference in DNA in these two types of heart Significant differences in RNA concentration in normal hearts from area to area shows that the left atrium tends to behave somewhat similarly to the left ventricular muscle and that the concentration of RNA apparently varies with pressure loading of each chamber of the heart In the hypertrophied heart there appears to be a significant increase in the concentration of RNA

I wish to thank Mr Lee Booker who prepared tissues for the RNA studies and Mrs Helen Brown who prepared the Feulgen sections Mr Bryan Harris performed all statistical computations

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Case report

Congenital mitral insufficiency associated with a ventricular septal defect

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Congenital mitral valve defects are rare. Of the cases reported in the literature, mitral insufficiency is the most frequent and is usually associated with other cardiac malformations.[1] In such cases the medical manifestations are the same as those with the acquired lesion; however, the onset of symptoms is much earlier and there is no history of rheumatic fever.[2] Since the association of mitral insufficiency and ventricular septal defect seems to be very unusual, we present the clinical and pathologic findings in one case.

Case report

R. A., a 2-year-old boy, was admitted to the Institute of Cardiology for complete cardiac investigation in February, 1961. His past history revealed that his early growth and development had been essentially normal until the age of 3 months. At that time he was hospitalized because of marked dyspnea after an episode of acute bronchitis. A heart murmur was detected. He was rehospitalized at the ages of 7, 9, 11, and 20 months for episodes of pulmonary infection with heart failure. Subsequent to each of these episodes he became more symptomatic, so that at the time of his admission to the Institute he was experiencing not only dyspnea on exertion but paroxysmal nocturnal dyspnea, marked cough, and epistaxis.

On physical examination, the child weighed 78 pounds. The heart rate was 100 per minute and regular. The second pulmonic sound was accentuated and palpable. A loud systolic murmur was heard along the lower left border and was accompanied by a thrill. There was an apical systolic murmur with a thrill transmitted to the axilla and the back, as well as a short diastolic rumble at the apex. Blood pressure in the arms was 90/70 mm. Hg and 100/75 mm. Hg in the legs. There were a few râles at both lung bases. The liver was slightly enlarged. There was no cyanosis, clubbing, or peripheral edema. The pulses were normal.

The electrocardiogram (Fig. 1) revealed left atrial dilatation and biventricular hypertrophy. Roentgenographic examination (Fig. 2) showed marked cardiac enlargement with a cardiothoracic ratio of 11.5/17.5. The pulmonary conus was convex and there was accentuation of the pulmonary vascular markings. On oblique view and after barium swallow we noticed a marked left atrial dilatation.

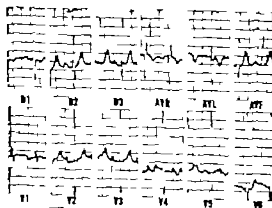


Fig. 1. Electrocardiogram taken on Feb. 27, 1961.

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Fig 2 Chest x ray films taken on June 22 1961 *Left* Anteroposterior view *Right* Right anterior oblique view



Fig 3 Left atrium The arrow shows the mitral cleft

Laboratory studies including hemoglobin hematocrit sedimentation rate white blood count and urinalysis were normal

Cardiac catheterization was performed (Table I) Right ventricular and pulmonary pressures were found to be at systemic levels There was a left-to-right shunt at the ventricular level The capillary pressure could not be measured

The diagnosis of ventricular septal defect with left-to-right shunt and systemic pulmonary pressure was thus established However because of the left atrial enlargement of a degree not usually seen with ventricular septal defect alone it was thought that there was an associated mitral stenosis contributing to the apical diastolic murmur

The child was discharged However the clinical condition became progressively worse and he was readmitted for surgery in June 1962 The physical examination was essentially unchanged He had lost 1 pound (he weighed 27 pounds) and the liver was palpable 2 fingerbreadths below the right costal margin

Surgical findings On June 27 1962 an operation for correction of the congenital cardiac lesions was undertaken with cardiopulmonary bypass and moderate hypothermia A marked left atrial enlargement was noted with an intra atrial systolic pressure of 30 cm The investigation of the mitral valve with the index finger did not reveal any stenosis The ventricular septal defect was closed by a prosthesis The immediate postoperative course was uneventful but the child died suddenly 24 hours after operation The cause of death appeared to be a cerebral vascular accident

Pathological findings At autopsy there was a marked cardiomegaly predominantly of the left chambers Both atria were dilated the left one being



Fig 4 View of the left cavities *1* Mitral cleft *2* Ventricular septal defect

Table I Cardiac catheterization data obtained on Feb 18 1961 in Patient R A 2 years old

Location	*Pressure (mm Hg)*			*Oxygen saturation*
	Systolic	*Diastolic*	*Mean*	(%)
Superior vena cava				66
Right atrium	10	0		54
Right ventricle—inflow	95	5		74
Right ventricle—outflow	90	5		68
Main pulmonary artery	90	40	60	72
Right pulmonary artery	100	45		74
Left pulmonary artery	95	35	70	69

almost aneurysmal The endocardium of the latter was white and thick On the anterior wall there was a rough and reddish area suggestive of a jet lesion covered by an adherent clot The interatrial septum was intact The mitral opening had a circumference of 9 cm On the anterior leaflet of the mitral valve a cleft of 2 cm was present causing a major mitral insufficiency (Fig 3) Both leaflets were thick and on their free edges were small *fibrous nodules* at the origin of the chordae The tricuspid orifice had a circumference of 5 cm and the leaflets were also thick The right ventricular cavity was smaller than the left one with the thickness of the walls respectively 0 6 and 1 2 cm There was a 1 5-cm defect (Fig 4) in the membranous portion of the ventricular septum It was located posteriorly and closed surgically by a prosthesis The pulmonary infundibulum was slightly hypertrophied but not narrowed The pulmonary arterial and aortic diameters were 2 5 and 1 2 cm respectively Both pulmonary and aortic valves were normal The coronary ostia were normally located There was no anomalous pulmonary venous drainage and the vena cava was normally located Injection of water into the right carotid artery showed complete obstruction of the *intracerebral* segment although the left carotid artery was normally patent Both lungs were slightly congested The brain weighed 1 160 grams There was a slight *compression* of the cerebellar tonsils The circumvolutions were flattened Thus the major autopsy findings were a large posterior ventricular septal defect and a mitral insufficiency caused by a mitral cleft The cause of death appeared to be a cerebral thrombosis which was probably due to embolization

Discussion

The interesting feature of this case was the similarity of the clinical picture to that presented by a large ventricular septal defect alone However the severity of the symptoms and the early onset of dyspnea made us suspect that the septal defect was not the sole malformation The symptoms an apical diastolic rumble and the x ray evidence of a large left atrium were compatible with an associated congenital mitral stenosis The hemodynamic findings confirmed the ventricular septal defect and showed a high pulmonary pressure but it was not possible to register the wedge pressure However at operation the left systolic atrial pressure was 30 mm Hg

The pulmonary congestion with episodes *of acute pulmonary edema* was secondary to the high pressure in the left atrium When the mitral lesion is congenital the signs of pulmonary congestion occur very early Both mitral stenosis and mitral insufficiency may result in enlargement of the left atrium but it is more marked in the case of regurgitation If associated with ventricular septal *defect the enlargement* is earlier and more rapid because of the increased flow by the shunt at the ventricular level

Cases of congenital mitral insufficiency have been reported as the result of dilatation of the annulus ring fibrous deformation of the leaflet and anomalous insertion and shortening of the chordae tendineae[3] However most frequently congenital mitral insufficiency is due to a cleft in the anterior mitral leaflet This lesion rarely occurs alone but rather in conjunction with another congenital lesion such as *atrial septal defect of the* ostium primum type[4] Likewise it is always seen as an integral part of a common atrioventricular canal It is rarely associated with an atrial septal defect of the ostium secundum type or with a ventricular septal defect Such a combined malformation may be a part of the spectrum of an endocardial cushion defect On the basis of our experience and

the cases reviewed in the literature we preferred to report our findings as a rare combination of two anomalies The surgical correction of the lesion depends upon the morphology of the anomaly[8] A mitral cleft can be repaired by suture of the edges

Despite the rarity of associated congenital mitral insufficiency and ventricular septal defect we think that the lesion could have been suspected clinically on the basis of the apical systolic murmur and thrill which were well transmitted to the axilla and the back along with the tremendous enlargement of the left atrium In the majority of the cases described in the literature there was also a diastolic rumble

Summary

We have reported the case of a 2 year old boy with congenital mitral insufficiency and ventricular septal defect Symptoms began in early infancy with severe progressive dyspnea on exertion episodes of pulmonary congestion and bronchitis The child underwent operation with correction of the ventricular septal defect but unfortunately he died 1 day postoperatively of a cerebral vascular accident

The rarity of this congenital syndrome is the main reason for our presenting a description of it A correct diagnosis seems to be feasible

We wish to thank Mr Jean Gauthier medical photographer of the Montreal Institute of Cardiology for the illustrations

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On sudden death

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But Peter said Ananias you have not lied to men but to God When Ananias heard these words he fell down and died

The Acts 5.3-6

Lear Pray you undo this button thank you sir Do you see this? Look on her look her lips Look there look there He dies

Edgar He faints! My lord my lord!

King Lear Act V Sc III

the awful suddenness—Life struck sharp on Death

William Osler

These three passages from man s inscribed heritage give dramatic expression to the fact of sudden death Ananias had broken faith with God under the pressure of Peter s confrontation he dies King Lear had trod the long and weary road from the realm of autocratic self indulgence to a new world that knew compassion and devotion only to find these newly acknowledged virtues exposed in the execution of Cordelia to a stress unbearable Having

> killed the slave who was a hanging thee

the old man struggles across the field bearing the lifeless body of his daughter hoping she yet may live Convinced at last that he has lost her he falls dead bating as Kent expresses it

> him
> That would upon the rack of this tough world
> Stretch him out longer

But it is Osler s phrase which epitomizes the physician s sense of frustration and futility as he encounters this all too common phenomenon of his practice the awful suddenness of Life struck sharp on Death

Sudden versus not so sudden death The role of cardiac disease

The moment of death universally is defined by an enduring cessation of the heartbeat Consciousness can persist but a few seconds beyond the moment of arrest of effective cardiac function and respiration for only a little longer Sudden death implies interruption of these processes whether from natural or unnatural causes abruptly and at a moment not precisely anticipated A corollary to these definitions is the proposal that more or less instantaneous death from natural causes can result only from abrupt cessation of effective cardiac function

Standing a measure apart from these concepts are certain statistical studies of coroners cases wherein sudden death is so defined as to include those victims who were apparently healthy at the time

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*Table I. 2 030 cases of sudden death**

Cause of death	*Per cent of deaths*
Coronary artery disease	30.4
Lobar pneumonia	8.7
Bronchopneumonia	6.5
Syphilitic aortitis	5.3
Valvular disease	4.1
Cerebral hemorrhage	5.4
Subarachnoid hemorrhage	4.6
Meningitis	1.9
Miscellaneous	33.1

*Adapted from Helpern and Rabson,[3] Table 2, page 1198, "Sudden and Unexpected Natural Death," published in the New York State Journal of Medicine, Volume 45, June 1, 1945, and reproduced with the permission of Dr. Helpern and the publisher.

*Table II. 1 000 cases of sudden death**

Cause of death	*Approximate number of cases*
Unrecognized heart disease	350
Nontraumatic intracranial hemorrhage	91
Meningococcemia	110
Miscellaneous, principally infections of the respiratory tract	300
No evident cause	140

*Adapted from "Sudden and Unexpected Death of Young Soldiers," by A. R. Moritz and N. Zamcheck, published in the Archives of Pathology, Volume 42, November 1946, and reproduced with the permission of the authors and publisher.

of death and where death took place usually within 24 hours after the onset of symptoms.[3] In many instances such deaths are not immediate or instantaneous, but occur with varying rapidity from a few minutes up to 24 hours or more after onset of illness.[4] A series of 2 030 cases of sudden and unexpected deaths so defined occurring in the Borough of Manhattan was compiled by Helpern and Rabson.[3] Distribution of cases according to cause of death was as shown in Table I.

A series comparable as regards definition of sudden death, but quite different in respect to population studied, was analyzed by Moritz and Zamcheck.[4] Their cases were derived from material at the Army Institute of Pathology and included only soldiers between 18 and 40 years of age. Only estimates were made of total number of deaths in each of five categories. Among 1 000 cases, approximately 350 died of unrecognized heart disease, 91 of non-traumatic intracranial hemorrhage, 110 from meningococcemia, and 200 to 400 from miscellaneous causes, principally infection of the respiratory tract. Finally, in 140 carefully investigated cases post-mortem findings were essentially normal. (See Table II.)

In these studies of Rabson and Helpern and of Moritz and Zamcheck, less than half the cases of sudden death, broadly defined, were ascribed to cardiac causes; however, in both studies, when the authors redefined sudden death as a more or less instantaneous event, cardiac disease became almost the sole cause, or almost the sole cause in cases in which any organic disease conceivably related to death was defined at necropsy.*

Sudden death: The anatomic lesion

Thus, review of the findings at necropsy in patients whose sudden death appropriately was ascribed to cardiac disease supports two points. These are: First, although rheumatic and syphilitic heart disease sometimes eventuated in sudden death, coronary sclerosis was the usual pathologic process encountered among patients so dying. Sixty-six and three tenths per cent of deaths from disease of the heart and aorta in the Rabson and Helpern series[3] and about 85 per cent of sudden deaths in the Moritz and Zamcheck series[4] were from coronary atherosclerosis. Second, fresh thrombosis of a coronary artery and acute myocardial infarction were present in only a minority of these cases in which sudden death was ascribed to coronary disease. Data derived from the study of 617 instances of coronary sclerosis in the series of Rabson and Helpern[3] are presented in Table III. Similarly, among the 115 cases of coronary disease selected for study by Moritz and Zamcheck, 31 had coronary

*This latter study did include 93 sudden deaths which occurred within a few minutes or less and in which the post-mortem findings were essentially normal. This group of cases will be considered after the extended discussion of cardiac disease as a cause of sudden death.

thrombosis 23 had obliterative atherosclerosis and 61 had severe but nonocclusive arteriosclerosis Myocardial infarction was present in only 22 of the 115 cases and recent in but 15 of these In both series of patients dying suddenly of coronary disease the incidence of thrombosis approximated only 25 per cent and of acute myocardial infarction something less than 20 per cent

Thus coronary sclerosis but not preeminently thrombotic or acute infarctive coronary disease is the most consistently occurring relevant anatomic finding in patients whose physiologic processes ceased with the abruptness properly warranting the designation sudden death

Sudden death The physiologic event

Novelty no longer would be manifest in berating the shoddy logic which suggested that the anatomic lesion in and of itself explained the physiologic event Both Weiss[4] and LeRoy and Snyder[5] have pointed out that among patients who die abruptly coronary arterial lesions are found which cannot be distinguished from similar ones in patients dead from other causes [3] Novelty would be abundant and rewarding however were that catastrophic termination of effective cardiac activity precisely delineated

Our remarkable ignorance of this terminal event stems not from want of interest in it nor from lack of efforts to obtain data which would clarify its nature Throughout several studies[6,7] concerned with the nature of terminal cardiac activity runs a persistent element of frustration for him who would know the exact character of the heart s action in individuals who are in apparent good health one moment and dead the next Patients included in these reported series almost invariably were sufficiently ill to be in a hospital Many had experienced acute myocardial infarction Others were in the terminal phases of congestive heart failure To derive from such data a conclusion that approximately half died in cardiac arrest and half from ventricular fibrillation would represent a reasonable approximation of the facts for patients so afflicted but such conclusion might have little relevance to the terminal event in the comparatively well person who dies abruptly

In the vanguard of sudden death Cardiac anoxia myocardial injury pacemaker or conduction arrest

Admittedly then available data do not establish the comparative incidence of cardiac arrest in relation to ventricular fibrillation on the other hand cardiac arrest *or* ventricular fibrillation almost certainly is the terminal event in these seemingly healthy individuals who die abruptly Moreover three elements are crucial in predisposing the heart to arrest or fibrillation and these are (1) cardiac anoxia (2) myocardial injury and (3) pacemaker or conduction arrest under the influence of increased vagal tone (or perhaps increased sensitivity to a usual level of vagal activity) The clarity of these simple proposals gives way to confusion as the search for rewarding clinical insights proceeds amid a dearth of precise data on the human heart which suddenly fails and the evident improbability that results of animal experimentation will duplicate the multiple combinations of cardiac anoxia myocardial injury and reflex imbalance which beset the diseased and aging human heart

Certain facets of knowledge derived from animal experimentation do merit review An article published by Harris[8] forms an appropriate prelude to consideration of the other studies performed by the same investigator in association with Moe and Wiggers

Harris experiments were conducted on both open-chest and closed-chest canine preparations He determined the conse

Table III *Sudden death from coronary disease Incidence of coronary thrombosis and myocardial infarction in 617 cases*

Coronary disease	*Per cent*
Nonthrombotic	73.3
Associated myocardial infarct	5.0
Thrombotic	26.7
Associated myocardial infarct	75.0

Adapted from Rabson and Helpern.

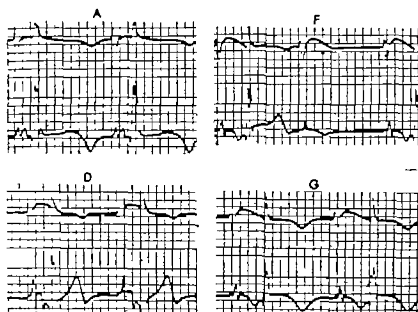


Fig. 1. Effects of severe hypoxia on the form and duration of changes in potential recorded at the A-V node (anesthetized calf, open-chest preparation). In each frame the upper trace was recorded with the exploring electrode on the anterior surface of the right atrium. The lower trace was derived from a needle exploring electrode placed with its uninsulated tip resting in the substance of the atrioventricular node. Frame *A* was recorded under conditions of adequate pulmonary ventilation. The nodal potential is the rectilinear deflection between the sharply peaked P wave on the one hand and the much taller QRS complex on the other; the nodal deflection occupies the initial 0.035 second of the 0.06-second interval between the termination of P and onset of QRS. Between Frames *A* and *D* the source of artificial respiration had been interrupted for approximately 1 minute. The P-R interval has increased by 0.02 second and *the duration of the nodal deflection has increased also by exactly that amount*. Its form is now that of a ladle with an initial broad positive component followed by a sharp descending limb and terminal short upstroke. Frames *F* and *G* were recorded during the severe and terminal phases of asphyxia. The interval *between the termination of P and onset of QRS has increased an additional* 0.04 second between Frames D and F. The second atrial deflection in *F* is followed by an abortive nodal deflection unattended by QRS. In *G* the interval between the termination of P and onset of QRS reaches 0.14 second (second complex) and the nodal deflection has assumed a nondescript curvilinear form. In all frames roller speed was 100 mm. per second. Sensitivity was N/2 in all records except Frame *D*, where the lower record was made at N/1.

quences of anoxia induced by pulmonary ventilation with mixtures of gas containing 5 to 8 per cent oxygen, as well as the changes induced by hemorrhagic shock and by coronary arterial occlusion. In the anoxic dogs pacemaker stoppage or cessation of A-V conduction almost invariably was the first gross manifestation of cardiac failure detectable in the electrocardiogram. Ventricular fibrillation occurred prior to stoppage of the heart in 1 of 19 animals. In 9 dogs subjected to hemorrhagic shock, 7 failed by pacemaker stoppage, another probably so, and one in ventricular fibrillation. In contrast to the terminal events in anoxia and hemorrhagic shock were those which occurred after abrupt occlusion of the anterior descending branch of the left coronary artery. In 25 of 50 animals so treated ventricular fibrillation developed, and in 4 more animals this arrhythmia occurred upon release of the clamp occluding the coronary artery. That ventricular fibril-

lation is the terminal arrhythmia in sequence to sudden occlusion of a major branch of the coronary arterial system is an observation amply substantiated by the results reported by other investigators those of LeRoy and Snyder[4] and of Manning McEachern and Hall[10] constituting two extensive series The incidence of ventricular fibrillation is closely related to the degree of compromise imposed on the coronary circulation as determined by the size of the vessel occluded The time of its occurrence usually is within 15 minutes after induction of occlusion and the animal which survives this period is unlikely to develop fibrillation However sudden release of occlusion was noted to produce another period of increased vulnerability to fibrillation

Significant electrophysiologic events in cardiac anoxia and myocardial injury

Certain limited evidence has accumulated concerning the nature of the electrophysiologic changes which attend these terminal disturbances of rhythm One development which forms a prelude to cardiac arrest under conditions of severe anoxia is illustrated in Fig 1 The electrocardiograms reproduced were recorded on a calf subjected to anoxia [11] A needle exploring electrode had been placed with its uninsulated tip resting in the atrioventricular node The nodal potential is the curvilinear deflection between the P wave and the QRS complex (See lower trace in each strip) Notable is the fact that changes consequent to anoxia are reflected solely and specifically in that nodal potential the electrocardiographic manifestations of atrial and ventricular myocardial excitation remaining unaltered

Evidence bearing on the electrophysiologic phenomena associated with initiation of ventricular fibrillation was supplied by Moe Harris and Wiggers (1941)[12] Working with canine hearts they found that a brief strong shock initiated at a time coincident with the vulnerable period of late systole or very early diastole produced tachysystolic beats and fibrillation But why did it do so? They concluded as follows We have presented evidence that a late systolic shock is really effective because it creates a tissue polarization of sufficient strength and duration to excite at the very first moments of the relatively refractory period Moreover it appears to start the rhythmic center from which several impulses are discharged at an accelerating rate the limit of the interval being about 80 msec These successive stimuli arrive at more remote regions later and later The progressive decrease in refractory periods associated with accelerating rate of responses combined with the delay in conduction furnish ideal conditions for re-entry of impulses but only after the second third or fourth truly premature beats have run their course After such a sequence of three or four increasingly premature beats ventricular fibrillation may begin

In 1943 Harris and Guevara[13] published recordings of the ventricular action potentials associated with ventricular fibrillation induced by acute coronary occlusion in 15 dogs and 1 monkey Fibrillation was introduced by an accelerating series of ventricular ectopic beats as previously observed in fibrillation from electric stimuli of various forms They observed also that in a local lead contiguous bipolar in type from the ischemic nonischemic borders potential spikes from ventricular activation four times normal height were sometimes recorded The highest spikes occurred at the time of most rapid tachycardia or slightly before Harris and Guevara concluded that the striking similarities between rhythms developed by regional ischemia and by application of galvanic currents suggest that the fundamental processes producing the rhythms and fibrillation by the two procedures may be identical in nature that fundamental process being the existence of a potential of comparatively high voltage created by electric shock or by a high boundary action potential

Brofman Leighninger and Beck[14] have expressed the concept of the ischemic boundary as the triggering zone for fatal cardiac arrhythmia (i e ventricular tachycardia) in the phrase current of oxygen differential this current giving rise to electric instability of the heart They proposed It is this instability due to unequal distribution of coronary blood

flow which appears to be responsible for the majority of deaths in patients with coronary disease A more nearly even distribution of coronary flow would prevent formation of these trigger zones between anoxic and well oxygenated myocardium and thus maintain electric stability of the heart They concluded that Any procedure such as the Beck I operation which safely and effectively produces intercoronary channels would tend to prevent or reduce this electric instability

Recently Jacobson Schiess and Moe[14] have reported that reduction of oxygen concentration of inspired air to levels between 5 and 10 per cent decreased the frequency of idioventricular discharge after ligation of a major branch of the coronary arterial system They suggested that Even though there can be no doubt that the potential gradient and flow of current engendered by ischemic injury must influence the excitability of marginal areas of muscle it is by no means certain that the flow of current is of itself the trigger which sets off spontaneous activity Hypoxia also shortens the refractory period of ventricular muscle and it is possible therefore for hypoxic but still viable cells to be re excited by adjacent normal tissue Whether the flow of current or the disparity of refractory periods is the prime agency exposure of the nonischemic area of muscle to hypoxia should be expected to reduce the difference between the perfused and nonperfused tissues and thus reduce the likelihood of spontaneous activity

In summary the following comments are pertinent to the nature of phenomena induced by anoxia hemorrhagic shock and acute localized myocardial ischemia or injury events which form a prelude to terminal cardiac arrhythmias general anoxia and hemorrhagic shock result predominantly in disturbances of pacemaker and A V nodal function significant forerunners of cardiac standstill localized myocardial ischemia or injury on the other hand predisposes to extrasystolic arrhythmias which prematurities in rapid sequence may lead directly into ventricular fibrillation Reduction of boundary potential between better and less well-oxygenated myocardium can be effected by a moderate reduction of oxygen content in inspired air, a procedure attended by decreased frequency of idioventricular activity

Autonomic reflex phenomena Sudden death as fatal syncope

To the evident possibility of coexistence in a clinical setting of anoxia shock and myocardial injury must be added another participating variable namely the consequences of phenomena which are reflex in origin The influence of vagal effects on sinoatrial and A V nodal function needs no elaboration Relevant to efforts designed to analyze events leading to catastrophic cardiac arrhythmias are two observations

1 Harris[9] noted that the disturbance in A V conduction and pacemaker function which occurred in 70 anoxic dogs during a period when the level of blood pressure remained normal could be relieved by severance of the vagus nerves Such disturbances could not be so relieved after the blood pressure had fallen to levels of 30 mm Hg or lower

2 LeRoy and Snider[8] reported that bilateral removal of the stellate ganglion and upper thoracic sympathetic ganglia reduced the mortality after acute coronary arterial ligation in the conscious dog from 75 per cent in a control series to 10 per cent in the group subjected to these neurosurgical destructive procedures

These studies suggest that the risk both of cardiac arrest and ventricular fibrillation within the heart predisposed to such arrhythmias by coronary disease may be potentiated by events of reflex type Pursuit of this concept leads directly to the possibility that fatal arrhythmias may develop solely as the consequence of reflex phenomena in a heart that is morphologically normal The anatomy of sudden death which heretofore presented only trying inconsistencies and inadequacies would so achieve ultimate elusiveness by ceasing altogether to exist Dr Soma Weiss[3] invoked exploration of this possibility when he noted Our observations indicate that instantaneous death is usually cardiac in origin and that its occurrence depends upon an underlying physiologic mechanism There is a close similarity and interrelation between the mechanism of instantaneous death and that of syncope

frequently indeed instantaneous death is merely fatal syncope *

Facts leading deeper into such conceptual territory were presented by Moritz and Zamcheck[4] who found among the approximately 1 000 protocols from necropsies on military personnel between the ages of 18 and 40 years a group of at least 140 carefully investigated sudden deaths in which the postmortem findings were essentially normal Ninety three of this group survived only a few minutes or less Only 16 showed occasional small intimal plaques in the coronary arteries instances of more significant coronary arterial changes being rejected from this group Characteristics of the fatal seizures witnessed in 96 of the 140 patients in the following group were as follows simple syncope (rarely preceded by vomiting or followed by labored respiration) 68 cases convulsions 17 cases substernal or epigastric pain and syncope 9 cases headache and syncope 2 cases not known or not recorded 44 cases

The pathologic changes observed in these cases generally were of agonal type and were not adequate to account for death The most frequently encountered change was cardiac hypertrophy (over 400 grams in 18 cases) In only one instance did the weight of the heart exceed 450 grams and here accompanying diffuse vascular disease existed

Moritz and Zamcheck concluded There is little to be said in summary of the pathologic observations of this group other than to reiterate that the methods of examination available to the pathologist (or the toxicologist) are frequently inadequate to disclose either the extent or the nature of certain disorders even though they (the disorders) are of sufficient severity to be incompatible with life

So this discussion reaches what is indeed a land of shadows exploration of which demands something more than increasingly intense application of traditional methods of pathology or physiology One may point admiringly to the freshness of approach represented in C P Richter's studies of sudden death in rats exposed to a life-endangering circumstance apparently devoid of possible escape and of tolerance to exposure to this same environment once the animal had experienced several episodes of successful escape * One may direct a puzzled eye toward the phenomenon of voodoo death but then move on to await accumulation of factual data commensurate with the abundant speculation of the past † For admittedly our course has led us to a point remote from the clinical commonplace of sudden death in the individual afflicted with organic heart disease to the bizarre phenomenon of sudden death apparently reflexly induced in one not predisposed to such catastrophe by a definable organic lesion But a fuller understanding of this latter phenomenon however rare might permit design of measures protective of those who otherwise will die prematurely with hearts diseased far less than the hearts of others who will survive for many years

Summary

1 When application of the term sudden death is limited to instances wherein death occurred more or less instantaneously and in some degree unexpectedly the vast majority of its victims will be found to suffer from organic heart disease predominantly coronary occlusive disease

2 In two major studies of patients dying suddenly of coronary disease the incidence of coronary thrombosis approximated only 25 per cent and of acute myocardial infarction something less than 20 per cent

*[illegible] cardiac hypertrophy [illegible] arterial [illegible] syncope [illegible] heart [illegible] arrhythmias.

*Of special [illegible] Richter [illegible] [illegible] parasympathetic [illegible] the heart [illegible] [illegible] experience.

† A bizarre [illegible] of death [illegible] ascribed [illegible] fright [illegible] reported by W B Cannon [illegible] [illegible] I fully agree with Dr [illegible] [illegible]

3 The presence of coronary occlusive disease does not per se explain why the afflicted individual should have died abruptly Others with lesions similar in kind and more extensive in degree may live on indefinitely

4 Although cardiac standstill and ventricular fibrillation are the established immediate causes of most instances of sudden death precise documentation of these events in clinical circumstances is lacking

5 Experimental studies of Harris Moe and others indicate (a) that general bodily anoxia and shock predispose to pacemaker arrest and A V conduction disturbances (b) that localized boundaries of injury developing in sequence to severe coronary insufficiency are the sites at which tachysystole and fibrillation develop—probably as a consequence of production at these boundaries of high action potentials during the ventricular excitation process (c) that general hypoxia induced by lowering the content of oxygen in inspired air may diminish the gradient of concentration of oxygen at the boundary of injury and reduce the frequency of extrasystolic discharge (d) that autonomic reflex activity may play a major role in increasing the vulnerability of the heart both to cardiac arrest and ventricular fibrillation

6 Sudden death apparently does occur albeit infrequently in individuals whose hearts are morphologically normal thus recalling Dr Soma Weiss statement that There is a close similarity and interrelation between the mechanism of instantaneous death and that of syncope frequently indeed instantaneous death is merely fatal syncope

7 With obvious justification an increased understanding of these reflex phenomena which exert protection in one individual and facilitate death in another may be zealously pursued

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The cardiovascular manifestations of systemic lupus erythematosus

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The systemic manifestations of lupus erythematosus have been known since the turn of the century. Cardiac involvement by the disease was first stressed by Libman and Sacks[1] who described the associated nonbacterial endocarditis in 1924. The pathology of the cardiac lesions was described in detail by Gross[2] in 1932. Discovery of the lupus erythematosus (L. E.) cell phenomenon in 1948[3,4] greatly facilitated the diagnosis of the disease. Since that time a number of clinical and pathologic studies have been reported from various parts of the world including the northern and western United States,[illegible] England,[illegible] Mexico,[illegible] and Chile.[illegible] These studies have emphasized the high incidence and diverse nature of the cardiovascular manifestations.

A striking increase in the number of patients in whom systemic lupus erythematosus has been diagnosed has occurred in this institution in the past 15 years. We have been impressed with the frequency of cardiovascular involvement and have thought it to be worth while to analyze the clinical and pathologic findings in our patients from this standpoint. There seems to be a need for more studies of this type and no such large series has been reported from the southwestern United States.

The present study

Over a 15 year period (1945-1962), 162 patients have been treated in the University of Texas Medical Branch Hospitals with a final diagnosis of systemic lupus erythematosus. A careful review of the records disclosed that the diagnosis was well established in 142 patients of this group and these form the basis of the study. Sixteen of these patients had post-mortem examinations.

The L.E. test was positive in 95 (72.5 per cent) and caused suspicion in an additional 9 of the 131 patients in whom it was performed. To exclude false positive L.E. reactions no case was included in the series unless the clinical and pathologic manifestations justified the diagnosis.

The sex and racial distribution of the patients is given in Table I. Females constituted 86.6 per cent of the cases, an incidence comparable to most large series. About one third of the patients were Negro and this roughly approximates the incidence of Negro admissions to this hospital. We were unable to demonstrate any racial predisposition to the disease.

The age distribution is graphed in Fig. 1 and shows a maximal incidence in the third decade. However, the second, fourth, and fifth decades are well represented. The

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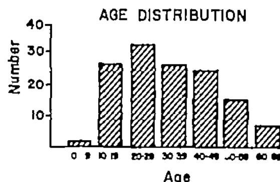


Fig 1 The cardiovascular manifestations of systemic lupus erythematosus

youngest patient was 8 years of age and the oldest was 67

Symptoms The frequency of symptoms listed in the chief complaint is shown in Table II One symptom was listed as the chief complaint in 55 patients two symptoms in 51 and three or four in the other 36 patients The most frequent symptom in the chief complaint was related to the joints and occurred in 56 per cent Fever was complained of in 33 per cent and a rash in 18 per cent Chest pain was listed as a chief complaint in 16 per cent of the patients but was usually of a pleuritic type Edema dyspnea and loss of weight were less frequent

In Table III are listed symptoms recorded in the total history of each patient The most frequent symptom was fever present in 82 per cent of the patients Joint symptoms most often those of an arthritis occurred in 76 per cent These usually simulated rheumatoid arthritis but were occasionally migratory in type A rash was noted by 56 per cent of the patients and was most often facial However at times it was generalized and ulcerations of the mouth were occasionally noted Chest pain occurred in 45 per cent of the patients and was of a pleuritic type in nearly *two thirds of these* In 6 patients the pain was classically anginal Loss of weight had occurred in 37 per cent and weakness in 35 per cent Dyspnea was complained of by 26 per cent of the patients but only 3 of 37 patients with this symptom had paroxysmal nocturnal dyspnea Edema occurred in 20 per cent and was due to congestive heart failure in 7 of 29 patients Alopecia had been noted by 13 per cent and convulsions had occurred in 8 per cent Raynaud's phenomenon was relatively infrequent and occurred in only 6 patients (4 per cent)

Laboratory findings Table IV lists the laboratory findings in this series of cases

Table I Sex and racial distribution of 142 patients

	White	Negro
Females 123 (86 6%)	83	40
Males 19 (13 4%)	14	5
Total 142	97	45

Table II Analysis of symptoms in chief complaint

	Number of patients		Per cent
Joint symptoms		79	55 6
Polyarthritis	62		
Polyarthralgia	17		
Fever		46	32 4
Rash		25	17 6
Chest pain		22	15 5
Edema		14	9 9
Dyspnea		8	5 6
Loss of weight		6	4 2

Table III Analysis of symptoms in total history of 142 patients

	Number of patients	Per cent
Fever	116	82
Joint symptoms	108	76
Rash	80	56
Chest pain	64	45
Loss of weight	53	37
Weakness	49	35
Dyspnea	37	26
Edema	29	20
Alopecia	18	13
Convulsions	11	8
Cough	11	8
Raynaud's syndrome	6	4
Myalgia	6	4
Ecchymoses	5	4

The most frequently positive laboratory finding was elevation of the sedimentation rate which exceeded 20 mm per hour (Wintrobe) in 93 per cent of the cases in which it was determined The hemoglobin level was below 12 Gm per cent in 87 per cent of the cases An increase in serum globulin to over 3 Gm per cent was found in 78 per cent and a decrease of serum albumin to below 3 Gm per cent in 55 per cent A white blood count below 4 000 per cubic millimeter was found in 48 per cent and the platelet count was below 100 000 per centimeter in 17 per cent The urine showed albumin (1 plus or more) in 69 per cent but this was often a transitory finding Hematuria usually microscopic was reported in 38 per cent There was azotemia with blood urea nitrogen values over 30 mg per cent or nonprotein nitrogen values over 50 mg per cent in 20 per cent of the patients A positive blood serology (Kahn) was found in 22 per cent of the patients but one of these had a history of syphilis

Physical findings Thirty-one (22 per cent) of the 142 patients had a persistent elevation of the diastolic blood pressure This was from 90 to 100 mm Hg in 15 patients from 101 to 110 in 4 from 111 to 120 in 8 and from 121 to 130 in 2 Two additional patients had diastolic pressures which exceeded 150 mm Hg and these had all of the physical and laboratory findings of malignant hypertension

Abnormal fundi were found in 30 patients (21 per cent) These were Grade 1 and 2 hypertensive in 14 Grade 3 in 3 and Grade 4 in 2 Exudates with cytoid bodies were noted in 13 patients and 1 patient had right optic atrophy

There was hepatomegaly in 38 patients (27 per cent) 7 of whom had right ventricular failure The spleen was enlarged to palpation in 27 patients (19 per cent) and there was lymphadenopathy in 42 patients (29 per cent)

Abnormal cardiac findings Table V lists the abnormal cardiac findings upon physical examination There was an increase in the cardiac dullness in 43 patients (30 per cent) and in 22 of these the point of maximal impulse was to the left of its normal position A pericardial friction rub was heard in 17 patients (12 per cent)

Table IV Laboratory findings

	Number of patients	Per cent
Anemia	123 of 142	87
Leukopenia	68 of 142	48
Low platelet count	15 of 86	17
Elevated sedimentation	119 of 128	93
Elevated globulin	108 of 138	78
Decreased albumin	76 of 138	55
Hematuria	54 of 142	38
Albuminuria	98 of 142	69
Positive serology	29 of 132	22
Azotemia	28 of 142	20

Table V Abnormal cardiac signs in 142 patients

	Number of patients	Per cent
Cardiomegaly	43	30
Pericardial rub	17	12
Ventricular gallop	16	11
Ejection murmur exceeding Grade 2	42	29
Regurgitant murmur exceeding Grade 2	6	4
Diastolic murmur	4	3

Table VI Electrocardiographic findings in 137 patients

T wave abnormalities	35
Abnormal S-T depression (undigitalized)	1
Atrioventricular block	6
Bundle branch block	5
Abnormal P waves	6
Left ventricular hypertrophy	8
Right ventricular hypertrophy	2
Pericarditis	8
Myocardial necrosis or scarring	4
Hypokalemia	3
Digitalis effects	3

An apical ventricular gallop was present in 16 patients (11 per cent) Most of the patients had at least faint systolic murmurs An ejection systolic murmur which exceeded Grade 2 (of 6) in intensity was heard in 42 patients (29 per cent) and was usually most intense over the apex A

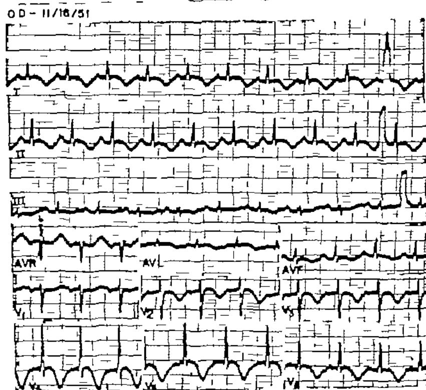


Fig 2 ECG of 35 year old white woman with clinical signs of pericarditis and myocarditis It shows sinus tachycardia diffuse ST T changes with slight S T elevations and prolongation of the Q T interval

mitral regurgitant murmur over Grade 2 in intensity was heard in 6 patients Diastolic murmurs were documented in 4 patients Two of these were considered to have aortic insufficiency Two patients had mitral diastolic murmurs but one of these had known pre existing mitral stenosis Moist rales at the lung bases were recorded in 10 patients (7 per cent) all of whom were judged to be in left ventricular failure

Electrocardiographic abnormalities Electrocardiograms were taken in all but 5 patients and in 118 patients more than one tracing was available Table VI shows the electrocardiographic findings The tracings were definitely abnormal in 59 of 137 patients (43 per cent) and were suggestively abnormal in an additional 12 (9 per cent)

Most of the tracings were concluded to be abnormal on the basis of *nonspecific* ST T changes found in 35 patients In 8 patients serial tracings showed classical ST T evolutionary changes of acute pericarditis Fig 2 is the electrocardiogram of a 35 year old woman who showed clinical findings of myocarditis and pericarditis The ST T configuration is compatible with subacute pericarditis and the myocardial involvement is *suggested* by the prolonged Q T interval Left ventricular hypertrophy was diagnosed in 8 patients and right ventricular hypertrophy in 2 Four patients showed abnormal S T depressions in the absence of digitalis or electrolyte disturbance Six others showed digitalis ST T effects QRS changes which were *considered to* be indicative of necrosis or scarring were noted in 4 patients The electrocardiogram of one of these a 26 year old white woman is shown in Fig 3 and was interpreted as recording a recent posterolateral myocardial infarction Later tracings showed typical evolutionary changes of such a process Bundle branch block occurred in 5 patients and atrioventricular block in 6 Six patients showed conspicuous P wave abnormalities These were indicative of left atrial enlargement

in 2 ST T changes of hypokalemia were found in 3 patients

Table VII lists the findings in an analysis of the QRS complexes Left axis deviation occurred in 13 and the QRS axis in these was from 0 to −30 degrees in 7 from −30 degrees to −60 degrees in 6 and from −60 degrees to −90 degrees in 1 Two patients showed right axis deviation the QRS axes being +120 degrees and +150 degrees Low voltage of the QRS complexes less than 5 mm in all limb leads was present in 23 patients The QRS duration of the 2 patients with left bundle branch block was 0 11 and 0 13 second The QRS duration of the 3 patients with right bundle branch block was 0 11 0 11 and 0 13 second The localization of the scarring or necrosis in 4 patients was anterior in 2 and posterior in 2

Disturbances in rhythm were infrequent except for sinus tachycardia which was found in half of the patients (Table VIII) One patient developed paroxysmal nodal tachycardia and another atrial fibrillation in the absence of the administration of digitalis or congestive heart failure Paroxysmal atrial tachycardia with atrioventricular block was recorded in another patient and was considered to be due to digitalis toxicity Premature ventricular contractions occurred in 5 patients Ventricular fibrillation was the cause of death in an undigitalized patient

Chest roentgenograms Chest roentgenograms were taken in 138 patients and cardiac fluoroscopy had also been done in 35 of these As shown in Table IX there were evidences of cardiac abnormality in 46 patients (33 per cent) and of pulmonary pathology in 66 (48 per cent)

Diffuse enlargement of the cardiac shadow was observed in 34 patients and the conclusion was that 12 of these had pericardial effusion Radiologic diagnoses of left ventricular hypertrophy were made in 8 patients and of right ventricular hypertrophy in 2 Three patients had a tortuous aorta and 3 showed left atrial enlargement

Pulmonary pathology was due to unilateral or bilateral pleural effusions in 32 patients and 20 had pulmonary infiltrates Ten of the 11 patients who showed evidences of pulmonary congestion had clinical

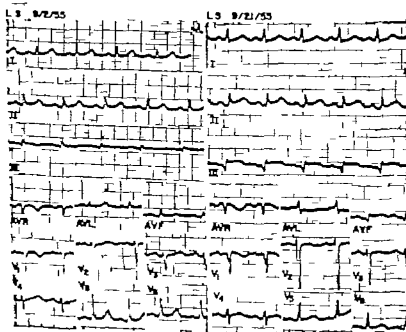


Fig 3 Electrocardiograms of 26-year-old white woman The tracing on the left is considered to be within normal limits The tracing on the right shows QRS and ST T changes compatible with acute posterolateral myocardial infarction

signs of left ventricular failure There were markedly increased bronchial markings in 6 patients and pulmonary atelectasis in 8 Two patients showed pulmonary fibrosis and right ventricular hypertrophy and were considered clinically to have chronic cor pulmonale Two patients showed moderate bilateral hilar adenopathy

Incidence and types of cardiac disease Abnormality of the heart was concluded to be present in 83 patients or 58 per cent (Table X) on the basis of clinical and laboratory evidences Hypertension was recorded in 31 of these patients (22 per cent) Congestive heart failure was diagnosed in 10 patients (7 per cent) being left ventricular in 3 and combined right and left ventricular in 7 *Staphylococcus aureus* endocarditis was engrafted on Libman Sacks valvulitis in 2 patients both of whom had received extensive steroid therapy

Myocardial disease was considered to be present in 47 patients (33 per cent) However it could have been secondary to hypertension in 10 patients and to coronary heart disease in 7 The cause of the myocardial abnormality in the other 30 patients (21 per cent) was apparently direct involvement of the myocardium by lupus erythematosus Such a conclusion was justified on the basis of the following findings in these patients (1) cardiac enlargement not due to hypertension valvular disease severe anemia or pericardial effusion (28 patients) conspicuous ventricular gallop not due to other causes (12 patients) and electrocardiographic abnormalities (30 patients)

Pericardial disease was diagnosed in 24 patients (17 per cent) on the basis of pericardial friction rub (17 patients) diagnostic evolutionary ECG changes (8 patients) and evidences of pericardial effusion (12 patients) In addition 1 patient developed constrictive pericarditis which was relieved by operation

Abnormality of the endocardium evidenced by signs of valvular disease was diagnosed clinically in 9 patients (6 per cent) The bases for the diagnosis were aortic diastolic murmurs in 2 patients mitral diastolic murmurs in 2 patients very loud mitral regurgitant murmurs in 3 patients without cardiac dilatation and loud ejection systolic murmurs in the aortic and mitral areas in 2 patients However 1 of these patients had known rheumatic mitral stenosis and 2 had bacterial endocarditis

Coronary artery disease was thought to be present in 7 patients (5 per cent) 6 of whom presented symptoms of classic angina pectoris and 4 of whom showed signs of necrosis in the electrocardiogram However the 1 patient of this group who died showed atherosclerotic coronary artery

Table VII Analysis of QRS complexes in 137 patients

Low voltage	23
Left axis deviation	13
Right axis deviation	2
Left bundle branch block	2
Right bundle branch block	3
Left ventricular hypertrophy	8
Right ventricular hypertrophy	2
Anterior scarring or necrosis	2
Posterior scarring or necrosis	2

Table VIII Cardiac mechanism disorders in 137 patients

Sinus tachycardia	68
Nodal tachycardia paroxysmal	1
Paroxysmal atrial tachycardia with atrioventricular block	1
Atrial fibrillation	1
Premature ventricular contractions	5
Ventricular fibrillation	1

Table IX Findings on chest roentgenograms in 138 patients

Cardiac pathology	46 (33%)
Diffuse cardiomegaly	34
Left ventricular hypertrophy	8
Right ventricular hypertrophy	2
Tortuous aorta	3
Left atrial enlargement	3
Pulmonary pathology	66 (48%)
Pleural effusion	32
Pulmonary infiltrates	20
Pulmonary congestion	11
Increased bronchial markings	6
Pulmonary atelectasis	8
Pulmonary fibrosis	2
Hilar adenopathy	2

disease as the cause of coronary thrombosis and myocardial infarction. Three of these patients were premenopausal normotensive women and in these the coronary involvement was suspected to be due to collagenous coronary arteritis.

Postmortem studies. Postmortem studies were performed on 16 patients, 12 of whom were females. Two of the patients were in the second decade, 5 in the third, 5 in the fourth, 3 in the fifth and 1 in the sixth.

The immediate causes of death in these 16 autopsied patients are listed in Table XI. The most frequent cause was congestive heart failure which occurred in 5 patients, 2 of whom had been mildly hypertensive. Two patients died as a result of endocarditis due to *Staphylococcus aureus* and both of these had received long courses of steroid therapy. One of these had ulcerative bacterial lesions on the mitral and pulmonic valves and the other had similar lesions on the mitral and aortic valves. Both showed abscesses in the viscera and 1 had a suppurative pericarditis. One patient with severe myocarditis but not in congestive heart failure died suddenly from ventricular fibrillation. The patient who died of a myocardial infarction was a mildly hypertensive 42 year-old man. Microscopic sections showed arteritis of the small coronary branches but the actual area of occlusion was the result of coronary atherosclerosis. Three hypertensive patients died of uremia and 2 of these showed typical manifestations of the nephrotic syndrome. One of the 2 patients who died of bronchopneumonia had received steroid therapy. The patient who died of shock after perforation of the esophagus had malignant hypertension and was on steroid therapy.

Cardiac pathology was shown to be present in all 16 of the autopsied patients (Table XII). Eleven of the patients showed evidences of pericarditis. This was acute serofibrinous in 5 with a volume of pericardial fluid of from 50 to 350 c.c. In 3 patients the pericarditis was acute fibrinous and no fluid was present. Suppurative pericarditis with 50 c.c. of purulent fluid was present in 1 patient with acute bacterial endocarditis.

Eleven patients had cardiac hypertrophy. This was confined to the left ventricle in 6 and was combined right and left ventricular in 5. The weights of the enlarged hearts varied from 265 grams (in a child) to 710 grams and 4 patients had hearts which weighed over 500 grams.

There were pathologic evidences of myocarditis in 13 of the 16 patients and it was considered to be severe in 6. Fig. 4 shows the microscopic section of the myocardium of a 38 year-old normotensive woman who died of congestive heart failure due to severe myocarditis.

Endocardial changes were found in 10 patients and these involved the valves

Table X. Clinical and laboratory evidences of cardiopathy

	Number of patients	Per cent
Myocardial abnormality	47	33
Pericardial abnormality	4	17
Endocardial abnormality	9	6
Coronary artery disease	7	5
Hypertension	31	22
Congestive heart failure	10	7
Bacterial endocarditis	2	1.5

Table XI. Immediate cause of death in 16 autopsied patients

Congestive heart failure	5
Bacterial endocarditis	2
Cardiac mechanism disorder	1
Myocardial infarction	1
Proteus septicemia	1
Uremia	3
Bronchopneumonia	2
Perforated esophagus and shock	1

Table XII. Cardiac findings in 16 autopsied patients

Pericarditis	11	
Cardiomegaly	11	
Left ventricular hypertrophy		6
Bilateral ventricular hypertrophy		5
Myocarditis	13	
Severe		6
Endocardial abnormality	10	
Valvular		8
Coronary arteritis	[illegible]	

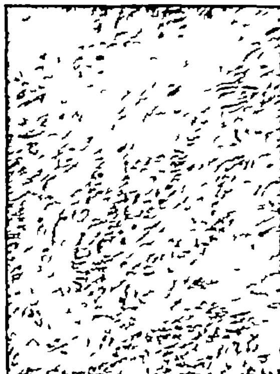


Fig 4 Low power section of myocardium of B B a 38-year-old normotensive woman who died of congestive failure due to myocarditis There is marked atrophy and replacement fibrosis of the heart muscle with extensive infiltration of polymorphonuclear leukocytes

(Libman Sacks endocarditis) in 8 Four patients had isolated mitral valve involvement 2 had lesions of both the mitral and aortic valves 1 had lesions of the mitral and pulmonic valves and 1 of the mitral and tricuspid valves In 2 patients the nonbacterial endocarditis was complicated by a staphylococcal infection One patient showed involvement of the endocardium without valvular changes and another showed similar isolated involvement of the endocardium of the right ventricle

Six patients showed coronary artery involvement by the disease process but no areas of infarction due to such an involvement were found The degree of coronary arteritis was considered to be extensive in 2 patients spotty in 3 and minimal in 1 The microscopic sections in 1 patient (Fig 5) showed a small thrombus in an area of arteritis but no area of infarcted myocardium was found

Pleural effusions were present in 6 patients and these were bilateral in 4 An other 2 patients showed evidence of pleuritis Nine patients had pulmonary edema 1 had pulmonary abscesses and 3 had bronchopneumonia Two patients showed small pulmonary infarctions Five of the patients had hepatomegaly and 6 had ascites which varied from 400 to 600 c c Splenomegaly was found in 6 and there was an abscess of the spleen in 1 patient with bacterial endocarditis Typical renal lesions of lupus erythematosus were found in 10 patients

Discussion

This study confirms the frequent involvement of the cardiovascular system in systemic lupus erythematosus There was clinical evidence of cardiac abnormality in 58 per cent of our patients an incidence similar to the 55 per cent reported by Harvey and associates[9] and 57 5 per cent by Robles Gil and associates[1] Other investigators have reported



Fig 5 High power magnification of small coronary artery F M W a 24 year-old woman who died of bronchopneumonia An organizing thrombus partially occludes the vessel the wall of which shows focal degeneration fibrinoid and round cell infiltration The nearby musculature showed mild myocarditis but no areas of necrosis

even higher incidences such as 70 per cent by Jessar and associates,[7] 81 per cent by Shearn[10] and 88.8 per cent by Armas-Cruz and associates.[12]

In only a minority of our patients were the symptoms on admission related to the cardiovascular system and this is contrary to the experiences of Shearn and Pirofsky.[4] Fever, arthritis, and rash were by far the most frequent presenting symptoms. Chest pain was usually of pleural origin but was at times due to pericarditis. Six of our patients complained of angina pectoris. Dyspnea was frequent but was usually explained by pulmonary pathology and paroxysmal nocturnal dyspnea occurred in only 3 patients. Edema noted by 29 patients was due to congestive heart failure in only 7. The incidence of Raynaud's phenomenon (4 per cent) is considerably less than the 6 to 26 per cent observed by others.[4,5] The relative infrequency of this symptom in our experience may be due to our hot, humid climate.

In 12 patients the presenting symptoms were dominantly cardiac with minimal or *no* evidences of the usual features of lupus erythematosus. In these cases the diagnosis was made only after a careful search for underlying causes of the cardiac manifestations. Six of these patients entered the hospital with acute pericarditis which initially was considered to be of the benign nonspecific type. Shearn[10] and Taubenhaus and associates[11] have stressed the importance of considering lupus erythematosus in such unexplained acute pericarditis, particularly in the female. Two patients were admitted because of massive pericardial effusions which required pericardial aspiration because of cardiac tamponade. Such large effusions are unusual in lupus erythematosus, but similar cases have been observed by others.[13,14,17] One unique case was that of a 28-year-old Negro man who developed the findings of constrictive pericarditis but also had minimal arthritis. Pericardiectomy resulted in excellent clinical improvement, but there was no evidence of specific etiology for the pericarditis. Later L.E. tests were consistently positive. Three of our patients who entered the hospital because of congestive heart failure were initially considered to have primary myocardial disease of unknown cause. The occasional role of systemic lupus erythematosus in producing such manifestations has been pointed out by Mattingly.[18]

Pericarditis was clinically diagnosed in 17 per cent of our patients, an incidence considerably less than the 48 per cent reported by Harvey and associates,[6] 36.6 per cent by Robles-Gil and associates,[1] 23 per cent by Jessar and associates,[7] and 31 per cent by Shearn.[10] We did not make this diagnosis unless there was a pericardial friction rub, evidences of pericardial effusion or constriction, or diagnostic ECG changes. Four of our patients were judged to have both pericarditis and myocarditis. Pericarditis was found in 11 of our 16 autopsied patients.

Myocardial disease was diagnosed clinically in 33 per cent of our cases and there was apparent primary myocardial involvement in at least 21 per cent. This clinical frequency approximates the 18 per cent of Dubois[9] and the 32 per cent of Shearn and Pirofsky.[4] It is less than the 43.3 per cent documented by Robles-Gil and associates.[1] Postmortem studies in our cases showed myocarditis in 13 patients, of severe grade in 6. In 5 of our autopsied patients myocarditis resulted in congestive heart failure, but hypertension contributed in 2 of these. Griffith and Vural[8] observed myocarditis in 14 of 18 cases studied post mortem, with congestive failure present in only 3.

Congestive heart failure occurred in 10 of our patients (7 per cent), 4 of whom were hypertensive. In 5 patients it was the immediate cause of death, and all of these showed pathologic evidences of severe myocarditis. Two of these patients had been mildly hypertensive, however. Congestive heart failure developed in 22 of 60 patients followed by Brigden and associates[11] and they considered the main cause of failure in their patients to be systemic hypertension. They saw no patients in whom myocarditis was the sole cause of failure and believed that other factors such as fever and anemia contributed significantly. Shearn[10] observed congestive failure in 15 of 83 patients and also concluded that hypertension and heart failure were significantly related in this disease. It is our conclusion that myo

carditis did play a dominant role in producing heart failure in at least 6 of our 10 patients This would agree with the findings of Harvey and associates [9] who observed that 8 of 9 such patients had good renal function and that myocarditis was the main factor contributing to failure

Hypertension occurred in 22 per cent of our patients and nearly half of these had diastolic pressures over 100 mm Hg Two of these had malignant hypertension Eight of our autopsied patients had a history of hypertension 3 of these died of uremia and 2 of congestive heart failure The incidence of hypertension documented in the literature varies widely from the 14 per cent of Harvey and associates[9] to the 44 per cent of Brigden and associates [11]

The clinical diagnosis of Libman Sacks endocarditis is difficult even if the patient is known to have systemic lupus erythematosus Systolic murmurs are frequent but there are numerous causes for these other than valvular abnormality such as fever tachycardia anemia and cardiac dilatation Diastolic murmurs usually signify valvular disease but these are rare and even when present they do not necessarily mean Libman Sacks endocarditis For the valvular disease may be of other etiologies such as rheumatic mitral stenosis in 1 of our patients and bacterial endocarditis in 2 others At autopsy Libman Sacks valvulitis was present in 8 of 16 patients and another 2 had endocardial but not valvular involvement by the disease This compares to the 8 of 18 cases reported by Griffith and Vural [4] and the 12 of 21 cases by Humphreys [14] The mitral valve was involved in all 8 patients who showed valvular disease and 4 had combined valvular disease Although the verrucae were originally reported most often on the tricuspid valve [1] recent studies generally concur with the high incidence of mitral involvement found in this series

The administration of steroids apparently had no effect upon the incidence of Libman-Sacks endocarditis found at necropsy as had been suspected by Shearn [10] In our autopsied cases steroids had been administered to half the patients with endocardial changes but to only 1 patient showing absence of these changes

Two of our patients who were not in congestive failure showed pulmonary fibrosis and infiltrations pulmonary hypertension and right ventricular hypertrophy There was no evident etiology for these findings except lupus erythematosus The high incidence of pulmonary involvement in this series agrees with the findings of Israel[15] and Gould and Daves [8] Shearn[10] did not observe cor pulmonale in his cases but 1 patient did show ECG evidence of right ventricular preponderance associated with pulmonary fibrosis Two patients reported on by Brigden and associates[11] had right ventricular hypertrophy due to extensive lung disease and the findings in 1 were confirmed at necropsy Robles Gil and associates[12] reported that in 3 3 per cent of 120 cases there was cardiopathy secondary to pulmonary hypertension It is apparent that although pulmonary manifestations are frequent in lupus erythematosus only occasionally is there severe enough pulmonary disease to produce pulmonary hypertension and right ventricular hypertrophy

Electrocardiographic abnormalities are frequent in this disease and parallel the incidence of clinical cardiac involvement An incidence similar to ours was found by Shearn [10] who recorded abnormal electrocardiograms in 45 of 73 patients The most frequent abnormalities are in the ST T waves which often reveal evidences of pericarditis and myocarditis There are numerous other contributing factors such as anemia electrolyte imbalance and drug therapy QRS changes of necrosis were found in 4 patients but the 1 who died was found to have underlying coronary atherosclerosis The cause of the QRS abnormalities in the other 3 patients is obscure and none had the clinical features of acute myocardial infarction Taubenhaus and associates[16] have pointed out that primary myocardial involvement by the disease may result in the development of circumscribed areas of necrosis to produce chronic infarct patterns in the electrocardiogram Although myocardial infarction has been documented in lupus erythematosus Shearn[10] has concluded that there is no proof that the pathologic changes associated with lupus erythematosus have ever resulted in the occlusion of a major coronary artery However coronary arteritis

which involved small branches was present in 6 of our 16 autopsied patients. Since the other 3 patients who showed apparent residua of myocardial infarction were all premenopausal normotensive women, it is to be suspected that coronary arteritis due to lupus erythematosus may be the cause of the changes.

The patients with congestive heart failure due to myocarditis generally responded poorly to management until steroids were added. The institution of such therapy usually resulted in improvement, and at times it was dramatic. However, this improvement was temporary, and within a year or two such patients died of refractory congestive heart failure. Pericarditis did not imply a poor prognosis other than that of the disease itself, and it usually responded well to steroids. The valvular lesions of Libman-Sacks endocarditis are small and do not interfere significantly with myocardial function. However, in an occasional patient, such lesions may be the site of localization of bacterial endocarditis.

The causes of death in lupus erythematosus have been dominantly cardiac and renal. Complications of steroid therapy also may play a considerable role in the development of terminal infections and apparently predisposed to bacterial endocarditis in 2 patients.

Summary and conclusions

1. An analysis has been made of the cardiovascular effects of systemic lupus erythematosus in 142 patients treated in the southwestern United States.

2. Cardiac pathology was found clinically in 58 per cent of the patients. There was clinical evidence of pericarditis in 17 per cent, myocarditis in 21 per cent, and endocarditis in 6 per cent. Hypertension was present in 22 per cent of the patients. Congestive heart failure occurred in 7 per cent and was usually due to myocarditis.

3. In 12 patients the presenting symptoms were dominantly cardiac, and only a thorough search revealed the underlying disease.

4. Electrocardiograms were definitely abnormal in forty-three per cent of the patients and were suggestively abnormal in another 9 per cent.

5. Chest roentgenograms showed evidence of cardiac abnormality in 33 per cent and of pulmonary pathology in 48 per cent.

6. Cardiac pathology was found in all of 16 autopsied patients, and in the various patients was found to involve all structures of the heart. Libman-Sacks valvulitis was found in 8 patients, and in 2 of these a staphylococcal endocarditis was superimposed.

7. The dominant cause of death in this series was cardiac, and 5 patients died of congestive heart failure. Other significant causes of death were renal involvement and infections which were predisposed to by steroid therapy.

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Alan F Lyon

Diuretic therapy
Part II Pharmacology of mercurial diuretics

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The diuretic effect of organic mercurials was discovered by accident when they were being used to treat syphilis in 1919 For the next 30 years they were the only important diuretics and still are a very useful part of diuretic therapy

Mechanism Despite their extensive use and considerable investigation the exact mechanism of action is still unclear Although the major action is on the kidney there may be some slight action on other tissues It has recently been noted that there is an increased flow of thoracic lymph after the injection of an organic mercurial in the nephrectomized animal This suggests a possible extrarenal basis for the mobilization of body water with resultant increased water diuresis after the injection of a mercurial diuretic Certainly no definite proof of a renal mechanism for this increased excretion of water has been offered The important natriuretic and chloruretic effects of the mercurial are definitely renal They are unassociated with increased renal blood flow or increased glomerular filtration rate and must reflect an effect on the renal tubules

The important action of mercurials has long been considered to be an inhibition of tubular reabsorption of chlorides This was based on the observation that (1) chloride is the ion excreted in greatest quantity during a mercurial diuresis and (2) the effectiveness of diuresis seems to be dependent on the level of serum chloride Thus mercurials become ineffective in clinical hypochloremic states and acidifying salts or carbonic anhydrase inhibitors that elevate the serum chloride often restore the potency of the mercurials Some authors have ascribed the potentiating effect of acidifying salts to an actual elevation of the urinary excretion of chloride prior to the mercurial rather than to a critical level of the serum chloride

The excess of chloride excretion over sodium excretion does not necessarily imply a primary chloride effect If sodium is the ion primarily excreted and chloride follows passively the normal operation of the distal tubular acidifying and potassium exchange mechanism will cause a greater reabsorption of sodium than chloride at this point and thus a greater chloruresis than natriuresis will result The relationship between the level and the effectiveness of chloride is not so clear cut as it first appears If acidosis is produced with ammonium nitrate as the acidifying salt potentiation may occur without effect on the level of the serum chloride whereas on the other hand in animals made hypochloremic but not alkalotic by the combination of infusion of bicarbonate and the

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breathing of carbon dioxide normal chloruretic effect will occur after mercurials Thus pH seems to be at least as important a factor as the level of chloride The strongest objection to the primary chloride effect of mercurials is the current physiologic concept of renal tubular electrolyte exchange which is based on the premise that the reabsorption of chloride is entirely passive

It is now generally accepted that the primary effect of mercurial diuretics is to block tubular reabsorption of sodium There is some uncertainty as to the exact site of action in the tubules since results obtained by various indirect methods such as the so-called stop flow techniques and histochemical methods are not comparable

It is of clinical importance that mercurials have a direct effect on the excretion of potassium When the excretion of potassium is high the use of a mercurial diuretic may actually suppress it apparently because of a secretion of potassium This may explain in part the lesser incidence of hypokalemic complication when mercurials are used alone to control the retention of fluid The intermittent nature of mercurial therapy may also protect against depletion of body potassium

Structure Most organic mercurial compounds with significant diuretic properties have chemical features in common The most important are a low dissociation constant and a rapid renal excretion These characteristics have been found to be associated with a chain of at least three carbon atoms with a mercury atom at the end of the chain

The general structure can be represented

$$R - CH - CH - CH_2 - HgX$$



OY

in which R X and Y are the three variables All three variables affect the activity of the compound The most important is R which is generally a complex organic radical either cyclic or often heterocyclic It is usually joined to the propyl side chain by an amide linkage At Y a methyl group is present in nearly all the commonly used mercurial diuretics Only in mercthoxylline is a different radical substituted

At X in all the commonly used parenteral diuretics except one theophylline is present In this complex with the mercurial radical mol for mol the amount of theophylline present has no diuretic activity when given intravenously Its effect is to produce less local irritation and better absorption from the site of injection than if the organic mercurial were given alone or with some other radical It may also accelerate the elimination of the mercurial by the kidneys

The ultimate biochemical effect of the drug is uncertain It is thought by some that a small amount of free mercuric ions is released in the renal tubular cell which then binds with enzyme sulfhydryl groups The fact that a mercurial diuresis can be almost instantaneously reversed by the mercury binding chelating compound dimercaprol (BAL) tends to support this Even if this is so it is not known whether this serves to interfere with the active reabsorption of sodium or whether it changes the character of the renal tubular wall and allows the back diffusion of electrolytes

Whatever the site and exact mechanism of mercurials it is a fact that parenterally administered organic mercurials are very potent natriuretic agents Although comparisons of potency are difficult to make and quite dependent on the method of comparison their effectiveness can be described by pointing out that at maximum effect a mercurial diuretic can cause a rejection of 20 per cent of filtered sodium whereas a maximum dose of a thiazide diuretic can produce about a 10 per cent rejection It is also of clinical importance that mercurials produce a true water diuresis *whereas the thiazides do not*

One parenteral diuretic mercaptomerin has as its substituent at the X position mercaptoacetic acid Although dithiol substituents such as dimercaprol may interfere with the effect of mercurial compounds on substrate sulfhydryl enzymes and thus block the diuretic activity monothiol substituents such as mercaptoacetic acid do not affect diuretic activity and seem to further reduce local irritation and cardiac toxicity

Chloromerodrin an oral diuretic which is rarely used now has like parenteral

mercurials a methyl group at the Y position but has the relatively simple urea radical at the R position and chloride at the X position rather than the theophylline

General toxicity All mercurial diuretics if given in excessive quantity to a patient with reasonably good renal function or in ordinary dosage to a patient with severe renal insufficiency can produce subacute mercury poisoning The first symptom is often a metallic taste Dissociation of the compound in the gastrointestinal tract produces stomatitis and colitis whereas excessive renal action can produce progressive renal insufficiency Chronic poisoning can be associated with anemia and peripheral neuritis Discontinuance of mercurial diuretic therapy and a course of intramuscular dimercaprol (3 mg per kilogram in 10 per cent solution given every 4 hours intramuscularly) may aid in preventing further damage

When given intravenously all mercurial diuretics have the potential probably on the basis of hypersensitivity of inducing a sudden cardiac death associated with shock and ventricular fibrillation Deaths from their intravenous use have been reported for all mercurial diuretics except mercaptomerin in which case the monothiol group may act as a protective agent Transient nonfatal shock like reactions can also occur with intravenous use

Other reactions apparently allergic both immediate and late can also occur These include flushing pruritis urticaria exfoliative dermatitis fever and nausea Neutropenia and agranulocytosis are rare

Symptoms may result from the profound diuresis which may produce transitory depletion of the extracellular space These symptoms include weakness muscle pains and cramps and even shock The hemoconcentration due to this depletion may also cause thromboembolic complications

Vigorous diuresis may cause some loss of potassium despite the fact that mercurials in themselves do not cause the loss of potassium that thiazides do In such instances patients on digitalis may develop toxicity

In patients with prostatism or other causes of poor bladder function the greatly increased urinary volume produced by the diuresis may cause acute retention of urine especially when the patient is at complete bed rest and under sedation

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Injections of adrenaline noradrenaline acetylcholine and pituitrin produced a fall in the intramedullary pressure and blood flow in bone. The effect lasted for several minutes after the arterial blood pressure had returned to normal. Injection of hexamethonium bromide caused a protracted fall in the intramedullary pressure and blood flow whereas histamine caused a rise in both.

No effect was observed on the blood flow or on the intramedullary pressure in bone after supramaximal stimulation of the peripheral cut ends of the femoral and sciatic nerves.

An increase in the intramedullary pressure and blood flow in bone occurred during active movement of a lightly anaesthetised cat's hind limb, which suggests that blood is squeezed out of the muscles into the bones. This may be a function of the osseomuscular circulation which Heald[9] has described. If a similar increase in blood flow and intramedullary pressure in bone occurs when limbs are actively moved under normal conditions it may be of profound importance. If the medullary cavity of bone can be considered to be a hydraulic damping system, such a system offers much greater mechanical strength than a simple structural arrangement can provide.

The present investigation has shown that in 90 per cent of 267 experiments a direct relationship existed between the intramedullary flow of blood and the medullary pressure; when the medullary pressure increased blood flow increased and vice versa. The medullary pressure can be assumed to be the resultant of the total flow of blood entering the bone and the total flow of blood leaving it, and it is suggested that the medulla behaves as a semiclosed cavity.

The intramedullary pressure in the tibial diaphysis of children with paralytic osteoporosis has been examined by a pressure transducer connected to the upper tibia by a saline filled cannula. Pressures which approximated the arterial blood pressure were found but in the tibia of normal children of the same age the intramedullary pressure was only about one quarter of the arterial blood pressure.

These observations on the flow of blood and on intramedullary pressure in bone are believed to have sufficiently far reaching implications to merit detailed study. Further investigations are in progress to examine the osseous circulation in normal and diseased states in man.

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Hypotension and coronary disease

Deaths from coronary disease in the postoperative period are not uncommon; surgeons generally welcome this finding because it would appear to indicate that the surgical management of the patient has been satisfactory. In 1939 Master Dack and Jaffe drew attention to the fact that in the Mount Sinai Hospital during the years 1931-1937 35 (5 6 per cent) of the attacks of coronary occlusion occurred after an operation in the hospital. The figure would have been higher but for the lack of proof in 13 additional cases. The control series consisted of the patients admitted to the medical ward for a variety of chronic illnesses; only 4 instances of coronary artery occlusion occurred in these in the course of 8 years. The authors considered a variety of reasons for the excess incidence in the postoperative period and concluded that the most important conditions were shock with the associated tachycardia, dehydration and changes in volume, speed, pressure and flow of blood in the coronary circulation.

In a series of 275 patients who died from coronary

thromboses on whom I performed a detailed microscopic examination, 122 were ward cases. Of these 122, no less than 25 had recently undergone major operations, some of them two in succession. Many of the operations were for such hypotensive episodes as accidents and massive hemorrhage from peptic ulcers. The 25 patients included those who were not in the immediate postoperative period; hence the figure is not very different from that reported by Master and associates. An additional 17 patients gave a history of recent hypotensive episodes, especially gastrointestinal hemorrhage and vomiting.

Findings such as these make it clear that states of shock can have an unfortunate effect on the coronary arteries; this does not appear to be open to controversy any more. Doubtless, the reason ascribed for the harmful effects will need further study.

In recent years the factors so long blamed for the development of coronary disease have been more and more disputed. It is now clear that there are certain parts of the coronary arteries which are especially vulnerable to disease, and other parts which are comparatively resistant. The descending branch of the left coronary artery is the most vulnerable. It is impossible to explain findings such as this from purely metabolic or biochemical studies. Although lipid undoubtedly accelerates the processes in many cases, other cases reach a fatal termination with very little lipid in the lesions. We must not regard coronary disease simply as a disorder of lipid metabolism.

The localization of lesions in the coronary arteries is well explained by studies in hemodynamics. These have been undertaken in three different ways: by Meyer, Texon and associates, by Murphy and associates, and by Osborn and Davis.[4,3]

How experiments explain the early, and many of the late, stages of coronary disease so well that it is difficult to avoid the belief that the *primary* factor in bringing about abnormalities of the coronary arteries is turbulent flow. Wherever an artery bifurcates there is a zone of physiological turbulence on the outer sides which may not cause trouble throughout a long life. It is evident, therefore, that an additional factor is necessary. This additional factor may well prove to be the shock state and other conditions which cause abnormal *ties of flow, such as dehydration, sweating* and vomiting. The zone of turbulence in the right side of the descending branch of the left coronary artery probably does not develop unless the blood flow is considerably reduced below normal. It is of course impossible for any experiment to reproduce exactly the conditions of flow in such a complicated structure as *the coronary artery*; only the simplest patterns have so far been examined, and this has been done for the most part on rigid tubes.

The evidence that the hypotensive state has a deleterious effect on the coronary arteries is many sided.

1. It is well known that if a patient remains in a hypotensive state after a coronary attack the prognosis is poor.

2. It has been found that an excessive *number of* patients who die from coronary disease have undergone major operative procedures, had accidents or been in other shock states in the comparatively recent past.

3. Good evidence is coming from a study of the patients who have died in spite of having lesions which were ideal for the anticoagulant therapy they were given. This study is not suitable for statistical investigation because the percentage of cases ideal for this treatment is relatively small. Thus, of the 225 patients, only 99 had thrombi in the main coronary trunks which could be proved in a study involving about 60 microscopic sections per case. Of the 99 patients, 36 were dead on arrival at hospital and had had no treatment. Thrombi may be *a trivial part of the whole pathologic process* or a major event; only the latter can be thought ideal for anticoagulant therapy. Twenty-four patients (10.7 per cent) of the cases had major thrombi but only 8 (3.1 per cent) were actually treated with anticoagulants. Thrombi may be primary, secondary or tertiary; they do not just happen but require a trigger *mechanism*. The primary thrombus is caused by a local trigger mechanism; this thrombus may be large, but is usually small and is already organizing when the patient first calls for treatment. The primary thrombus will be the trigger mechanism for the large secondary thrombus should that develop. The main aim of anticoagulation must be the prevention of secondary thrombi. Some cases in the series appear to prove that there is a critical level for prothrombin activity at about 22 per cent; above this the patient should be regarded as not on anticoagulant therapy. These patients were doing very well clinically with *prothrombin* activities between 10 and 20 per cent, but there was a slow, steady rise in this figure and death occurred when a large secondary thrombus developed as the prothrombin activity reached 24 per cent. It was found, however, that the problem is not so simple as this, and death may occur in spite of adequate *lowering of the prothrombin activity* in a case ideal for such treatment. An example of this was a 55-year-old man. On Aug. 21, 1961, he was treated by vagotomy and gastroenterostomy; progress was good and he was discharged from the hospital 11 days later. On September 8 he was readmitted as an emergency case because of anginal pain and breathlessness. He was treated with anticoagulants, but anginal pain recurred. His prothrombin activity was 28 per cent on September 11, 10 per cent on September 12, 10 per cent on September 13, and he died before the test could be repeated on September 14. He had a small primary and a large secondary thrombus. A case like this must mean either that anticoagulant therapy is useless or that it will be ineffective in ideal cases *in the presence of conditions such as anginal pain* with sweating, vomiting, hypotension, etc.

4. It is clear that clinical coronary disease is the end stage of a very long process. To determine the lesions of the long silent period it is necessary to take large numbers of cases from all age groups, particularly patients dying from accident and suicide. These young patients, like those dying from the disease, frequently show that the lesions *have built up in a series of phases. It is only possible* to suggest the cause of the first or last of these

phases the timing of the intermediate phases is too vague for any degree of certainty in explanation. A large fibrous phase and a small lipid phase corresponding in age with the 3 weeks between the accident and death is illustrated in *The Lancet*.[7]

5. Severe acute lesions of the coronary arteries have been recognized in patients dying after some hours of hypotension, e.g., in a 35 year-old woman who died 10 hours after removal of an eosinophilic adenoma of the pituitary, an operation which was performed with hypotensive anesthesia. The artery from that case is illustrated in Figure 167 (page 183) in *The Incubation Period of Coronary Thrombosis*. A second example is illustrated in Figure 36 (page 44) of the same text.[8] The latter example was from a 31-year-old boy who collapsed during an operation for brain tumor; he had been vomiting for 3 months before operation. Minor degrees of this lesion may well be reversible. The time needed to produce such abnormalities is being investigated; it may be over 2 hours.

The 122 ward cases were analyzed to see whether there was any difference in the history of hypotensive episodes between the 63 cases with thrombi and the 59 cases without thrombi. Absence of a history of hypotensive episodes was less common in those with thrombi (11 cases) than in those without thrombi (30 cases). The other big difference was in the history of anginal pain: this was prominent in 30 cases with thrombi but in only 9 without. There was little difference in the history of recent operations (12 and 13 cases respectively) and in the history of gastrointestinal hemorrhage, vomiting, and other hypotensive episodes (10 and 7 respectively).

Coronary disease may be silent long after the stage of secondary vascularization has been reached (10 born). At any time after a secondary blood system develops local vicious circles may cause the disease to progress in spite of all known therapeutic measures. Our best research project must be to learn all about the flow and other conditions which start and sustain the lesions which result in the development of secondary vascularization.

The pathology of the coronary arteries is very complex. Theories on etiology must not be held so strongly that unexpected findings which occasionally arise are not followed up. The discovery of lesions due to the hypotensive state was unexpected, but this should not have been so in view of the fact that it has been 25 years since Master and his co-workers drew attention to the association. We are bound to ask two questions: (1) How much of the increased incidence of coronary disease is due to conditions associated with the operations which have increased so greatly in frequency during the past 50 years? (2) How are we to prevent the ill effects of operation? The hypotensive state is so strongly suspect that pending final clarification of the problem, hypotensive anesthesia should not be used except when its advantages to the surgeon are so great that its use is justified.

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Estimation of plasma protein

Descriptions of analytical methods for plasma protein and discussions of their merits are widely distributed; they form an extensive literature which was last adequately reviewed by Salt. The Kjeldahl procedure has usually been assumed to give the truest protein values. However, this method may be no more reliable and frequently is less precise under hospital laboratory conditions than, for example, the rapid specific-gravity method in which small drops of serum or plasma are balanced in copper sulfate solution. Very good correlation between chemically assayed and specific-gravity derived results for protein estimations has been reported repeatedly by both European and American workers. Other workers have concluded that specific-gravity methods for serum protein are intrinsically unsatisfactory, but this view, which unfortunately is widespread, seems to be based on studies carried out with inadequate experimental techniques.[4] Certainly hypoalbuminemic

and hyperglobulinemia have no detectable effect on the relationship

$$\text{Protein} = 383 \, (\text{S G} - 1.007)$$

where S G is the specific gravity found by the technique of Phillips and associates. Furthermore there is evidence that the amino-acid N content of a globulin molecule (measured by Kjeldahl procedures) can be influenced by diet but not that such influence is reflected in the specific volume of the protein.

In the clinical consideration of a patient's plasma protein level the existence of an appreciable diurnal variation in the albumin concentration is frequently overlooked. The extent of this is from 2 to 8 Gm per liter (mean 5 Gm per liter) increasing during the day. Also relevant here are the errors inherent in the particular method used. Individual albumin determinations by either a standard biuret method[3] or by electrophoresis and dye binding have a precision of about ± 7 per cent. The precision of the total protein determination by the biuret reaction is about ±5 per cent and by the specific gravity method ±3 per cent. When there is the unavoidable error of a total protein and an albumin assay of a particular plasma being of opposite sign an inordinately large effect on the magnitude of the albumin-globulin ratio occurs because of the fact that the normal plasma A/G ratio is close to unity. This alone appears to be sufficient reason for discontinuing the custom of correlating the A/G ratio (rather than the albumin or the globulin level) with the patient's clinical state.

The large number of published articles in reference to paper electrophoresis of plasma proteins in no way reflects the value of the technique in assessing the clinical assessment of individual patients. In research on specialized proteins and on substances bound to proteins electrophoresis is of immense value but when applied to plasma protein estimation it is of disappointingly limited clinical value. With the great majority of patients it gives information which merely confirms what can be deduced from the results of simpler tests. Moreover the albumin and globulin concentrations obtained by paper electrophoresis are no more accurate and are frequently less accurate than those obtained by other fractionation procedures because the dye binding capacities of the individual proteins (used in their colorimetric estimation) alter in disease.

In hospitals (not served by chemical laboratories with mass automation) selective blood screening investigations for deranged protein metabolism may most usefully and economically be undertaken in the following order (1) total protein by specific gravity (2) quantitative gamma globulin and fibrinogen by turbidity tests (3) qualitative test for plasma proteins by thymol reaction. The rapid and accurate measurement of total protein in a patient's plasma—such as is given by the specific gravity—remains of particular value because it can give immediate information about the development and response to therapy of decreased extracellular fluid volume, dehydration, hemoconcentration and shock. Alternatively the finding of a low protein level will almost always be due to albumin deficiency which occurs in many conditions affecting the liver or the kidneys.

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Anemia and heart disease

In the assessment of a patient with heart disease it is important to consider anemia because anemia itself may bring about considerable disturbance in the circulation and may also aggravate or bring to light underlying cardiac disease. Whether the anemia is of the iron-deficient or the megaloblastic type and irrespective of its cause the resultant circulatory effects are the same. Where anemia is acute after hemorrhage or sudden rapid hemolysis the situation is usually obvious. The effects are those of a sudden decrease in the blood volume or of anoxia by reason of the rapid reduction in the circulating red cell mass.

Chronic anemia on the other hand may be more difficult to recognize. It is important however that it should be recognized because severe chronic anemia may affect the heart in three ways. It may produce a hyperkinetic state, it may cause or precipitate angina or acute coronary insufficiency, or it may result in nutritional degenerative changes

which affect the cardiac reserve. All these conditions arise from the deficiency of oxygen in the blood. The effects produced depend on the severity and chronicity of the anemia, the integrity of the myocardium, and the age of the patient. The hemodynamic disturbances are all compensating ones: in chronic anemia the increased cardiac output is maintained by tachycardia, by a raised venous filling pressure, or both. In general the velocity of the circulation rate of the blood flow is increased in proportion to the severity of the anemia, and there is evidence that the percentage utilization of oxygen is enhanced.

Only if the anemia is very long standing does the heart undergo dilatation and hypertrophy, and treatment of the anemia before this stage is reached will completely reverse the other disturbances. Electrocardiographic changes, such as low voltage complexes and T wave changes, can also be abolished by treatment. The reversal of the hemodynamic effects of chronic anemia has recently been well demonstrated by Roy and associates in 51 patients with anemia due mainly to ancylostomiasis who were studied before and after treatment.

Even a slight degree of anemia may lead to myocardial insufficiency when there is severe ischemic heart disease. However, anemia may cause angina when there is little or no underlying coronary disease, although probably only if the hemoglobin is under 4 or 5 Gm. per cent. Cardiac pain in anemic patients without any underlying disease of the coronary arteries has been recorded. Coombs[2] reported 8 cases out of 36, and Willius and Giffin[3] 43 (2.7 per cent) out of 1,360 patients with pernicious anemia. Nevertheless there is a certain amount of doubt about the degree of anemia necessary to produce cardiac symptoms. Many workers[4] consider that the hemoglobin usually has to fall to less than 7 Gm. per cent before any symptoms or signs are noted, but there are exceptions.

As Hunter[6] has pointed out, many anemic patients have cardiovascular symptoms (dyspnea on exertion, palpitations, syncopal attacks, edema, etc.) similar to those complained of by patients with organic heart disease.

Porter and Watson James[5] rightly emphasized that the potential ill effect of anemia on the diseased heart, on the senile heart, or on the heart laboring under the stress of hypertension, hyperthyroidism, valvular heart disease, pregnancy, or arteriovenous fistula, is a clinical problem of major importance. Relief of the anemia may be a deciding factor between recovery or continued cardiac failure. Anemia, whatever its underlying cause, is now relatively easy to treat, provided that the cause is discovered. Anemia in cardiac patients should first be fully investigated and then efficiently treated, and when this is done re-examination will frequently reveal that the condition of the heart is better than was previously thought possible.

In cases of iron deficiency anemia, after sources of loss of blood have been sought and treated, the dietary history considered, and if necessary the absorption of iron studied, treatment will normally be given in the form of iron by mouth or by injection. In pernicious anemia, when the diagnosis has been established by the typical blood picture, megaloblastic bone marrow, histamine-fast achlorhydria, and a low serum vitamin B_{12} concentration, replacement therapy by injection of vitamin B_{12} is a well established form of treatment. Recent work, however, has shown that vitamin B_{12} may be given by mouth, provided that it is given in sufficient dose. That adequate replacement is necessary from a cardiac point of view is suggested by the work of Jamal and associates, who have shown that vitamin B_{12} is important in the metabolism of the myocardium. Oral therapy gives a maximum reticulocyte response, effective and permanent elevation of hemoglobin and red cell count, and also maintains the serum vitamin B_{12} at a normal level. The neurological manifestations of a lack of vitamin B_{12} can also be alleviated.[10] A dosage lower than 300 μg daily may maintain a normal blood picture but it does not keep the serum vitamin B_{12} within the normal range. Treatment that does not do so should not be considered to be adequate.

Blood transfusion is, of course, a necessity in acute cases of anemia, whether due to hemorrhage or hemolysis, but in chronic anemia great care must be taken because of the risk that acute pulmonary edema may be induced by an ill-judged or ill-timed blood transfusion.

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Book reviews

HUMAN AGING: A BIOLOGICAL AND BEHAVIORAL STUDY. Edited by James E. Birren, Robert N. Butler, Samuel W. Greenhouse, Louis Sokoloff, and Marian R. Yarrow. Public Health Service Publication No. 986. Washington, D.C., 1963, United States Government Printing Office. 328 pages. Price $3.

This book represents the efforts of 22 contributors who present their data and ideas concerning various aspects of human aging. The book is published under the auspices of the National Institute of Mental Health of the National Institutes of Health. Many aspects of aging are discussed, including methods of study of aging of men, influence of aging on the cerebral circulation and metabolism, the electroencephalogram, psychomotor responses, auditory responses, mental testing, personality characteristics, and other aging phenomena. Obviously, a book of only 328 pages on such an expansive problem cannot be expected to be complete. Nevertheless, the chapters are interesting and the book is a good one.

ATHEROSCLEROSIS: MECHANISMS AS A GUIDE TO PREVENTION. By Campbell Moses, M.D., Associate Professor of Medicine and Director, Addison H. Gibson Laboratory, University of Pittsburgh School of Medicine. Philadelphia, Pa., Philadelphia, 1963, Lea & Febiger. 237 pages, 54 illustrations. Price $8.

The full title of this book is "Mechanisms as a Guide to Prevention." The author's objective is to provide for physicians with an interest in the problems of atherosclerosis a survey of present concepts of the mechanisms involved in its pathogenesis and thereby enable them to have a better understanding of present methods aimed at the prevention of atherosclerosis and its disastrous complications.

After a short chapter on the world-wide distribution of atherosclerosis, the first half of the book summarizes current knowledge and hypotheses about the biology of the process. In the longest chapter, on pathogenesis, the author distinguishes between local factors (the lipoproteins, collagen, elastin, fibrin, and the fibrinolytic system) and modifying factors (genetic, hormonal, stress, diet), both sets acting over a relatively long period of time. Although control of the lipoproteins is a prominent feature of current therapies, the author suggests that changes in the collagen content and the elastic properties of the arteries may be the basic mechanism. Subsequent chapters in this section deal with the distribution and severity of lesions in the principal arteries, the roles of cholesterol metabolism and the lipoproteins, the biosynthesis of steroid hormones from cholesterol, and hormonal factors that affect lipid metabolism. Thereafter the author moves on to consider the detection and prevention or ameliorative treatment of susceptible individuals. The relationships between atherosclerotic catastrophies and serum lipoproteins, body build, blood pressure, obesity, heredity, smoking, exercise, and emotional stress are reviewed in turn. The two final chapters discuss the principal hypocholesterolemic drugs and the question of dietary regimens.

For the physician whose primary interest is in what the book has to say about prevention and treatment, short summary statements appear at the end of most of the chapters in the second half. As might be expected in a book designed to give a balanced view of the subject, including its complexities, these recommendations are presented in rather general and conservative terms. For example (p. 185): exercise (at least in accustomed amounts) is probably good and certainly not deleterious. It probably never should be severe and unusual. Under no circumstances should severe and unusual exercise follow a deliciously fatty, generous meal. One recommendation (p. 147) is that serum lipid levels be determined routinely in the late teens or early twenties and at subsequent annual health examinations, especially if there is a family history of cardiovascular trouble, diabetes, obesity, or hypertension.

Needless to say, the book covers a wide range in a confusing field about which a great deal remains to be learned. The quality of the reviewing is excellent. The exposition is consistently clear. In areas of conflict the author's summary comments are forthright and judicious (although of course some protagonists may dissent). Documentation by references is thorough. Moreover, the author includes accounts of research and hypotheses which currently are not thought likely to provide leads to better understanding of the process but which might do so at some future time.

CONGENITAL ISOLATED VENTRICULAR SEPTAL DEFECT: HEMODYNAMICS, CLINICAL FEATURES, AND PROGNOSIS AFTER THE AGE OF TWO YEARS. By Erik Sandor, M.D. Copenhagen, 1963, Munksgaard. 218 pages.

In this monograph the author presents data obtained from 87 patients with ventricular septal defect who were studied by right heart catheterization from 1947 through 1960. The patients were all over 2 years of age and had medium to large defects. In each study the diagnosis was established by the oxygen step-up method.

The monograph is divided into several sections. In the first section there is a review of the history of ventricular septal defect and an extensive mathematical exegesis of the hemodynamic terms employed by the author. A second section deals with the correlations of hemodynamic, electrocardiographic, phonocardiographic, roentgenographic, and pathologic data. The cor-

relations presented in the second section are confirmatory and present no serious discrepancies from the body of literature previously published on ventricular septal defect. The hemodynamic correlations in particular suffer considerably because of the lack of measurements more precise than the oxygen method for determining flow and shunts. Acceptance of an average figure for oxygen content from two samples of blood from the superior and inferior vena cavae as the average oxygen content of venous returning blood presents a considerable problem of adequate mixing. Shunts calculated on this basis alone can be grossly incorrect and may be quite misleading. The criterion of venoarterial shunt employed by the author is that the arterial oxygen saturation be less than 93 per cent with the patient breathing ambient air. This measurement does not consider respiratory factors such as sedation, even mild sedation, which frequently depress oxygen saturation to levels below 93 per cent even without an intracardiac venoarterial shunt. Calculation of the magnitude of venoarterial shunts on the basis of that single criterion will overestimate the incidence and magnitude of venoarterial shunts and present serious problems in the acceptance of the author's hemodynamic correlations. It is clinically expedient although not always exact to use pulmonary wedge pressure as a measure of left atrial pressure and pulmonary vascular resistance. The author attempts from these measurements of pulmonary vascular resistance to determine what the "natural" resistance would be if he subtracted the shunt from the systemic blood flow. The vascular resistance naturally rises as the flow falls, but even this is not a straight line relationship. The concept of natural resistance obtained in this method is open to much question.

For these reasons this volume is not to be highly recommended as a teaching book.

SURGERY IN WORLD WAR II. THORACIC SURGERY. Volume I. Edited by Col. John Boyd Coates, Jr., MC, USA, Frank B. Berry, M.D., and Elizabeth M. McFetridge, M.A. Washington, D. C., 1963, Office of the Surgeon General, Department of the Army. 394 pages.

This is the first of two volumes dealing with thoracic surgery in World War II and is a part of the Professional Series of the Official History of the Medical Department of the United States Army in World War II. The series serves a three-fold purpose: it records historical developments in military surgery during World War II; it provides a guide for military surgeons in formulating policies and procedures to meet existing and future need; and it is a reference work for those surgeons engaged in civilian practice of surgery.

The present volume begins with a historical account of thoracic surgery by Dr. Frank Berry. For the teacher and the thoracic surgeon this section of the volume is invaluable. Developments in thoracic surgery from the time of the ancients is included, but this section is of particular interest because it reviews the management of thoracic wounds in World War I and emphasizes how little was known about pulmonary physiology and thoracic anesthesiology at that time. In spite of inadequate knowledge, certain basic principles in the management of thoracic wounds had evolved by the end of World War I, and the fact that they were not applied more often was due to the lack of equipment and trained anesthesiologists for endotracheal anesthesia and to the scarcity of trained thoracic surgeons. As Dr. Berry clearly points out, the great strides made in thoracic surgery between World Wars I and II should have effected correction of all the major deficiencies existing during the first of these conflicts and should thus have led to sound and effective treatment of thoracic wounds from the outset of World War II. That this was not the case is evident from this volume, for many of the lessons learned in World War I had to be relearned in World War II. It is hoped that the comprehensive, detailed, and frank account of surgical experiences in World War II presented in this series will preclude any such recurrences.

The present volume includes a section concerned with administrative considerations in cases of wounds of the chest, such as evacuation and transport equipment, blood supply, hospital installations, and thoracic surgery centers. The remainder of the volume, which is of particular interest to the surgeon today, is devoted to the general management of wounds of the chest. The evolution of the clinical policies in the Mediterranean theater of operations is reviewed in detail, since these served as a model in other theaters of operation. The emergency management of chest wounds, resuscitation and preoperative preparation, initial and reparative wound surgery, and reconditioning and rehabilitation are described in detail. The chapter on anesthesia is disappointing in view of the important role that anesthesia played in the development of thoracic surgery in World War II. One wishes that the author of this chapter had elaborated on the experiences in the North African and Sicilian campaigns when equipment was inadequate and trained anesthesiologists were few. This volume should prove to be useful not only to the military surgeon but to the civilian thoracic surgeon as well.

DRUGS OF CHOICE 1964-1965. Edited by Walter Modell, M.D., Associate Professor of Pharmacology, Cornell University, Ithaca, N. Y. St. Louis, 1964, The C. V. Mosby Company. 1018 pages. Price $16.75.

This is a good book which contains discussions of the pharmacology and therapeutic aspects of the choice drugs available in 1964. Many prominent pharmacologists, clinicians, and anesthesiologists are contributors. Among the subjects

that the patient had been catheterized and pressure data are reported.

A brief description of the findings precedes the detailed analyses of individual clinical cases.

It is unfortunate that no bibliography and no index have been prepared. Also a brief clinical summary of each case would have increased the the value of this work.

The illustrations are first class.

In conclusion, this is a valuable book for students in the field.

MODERN TRENDS IN DISEASES OF CORONARY ARTERIES AND ISCHEMIC HEART DISEASE. Edited by Charles K. Friedberg, M.D. and Ephraim Donoso, M.D. New York, 1964, Grune & Stratton, Inc. 316 pages. Price $11.75.

This publication consists of 16 papers which appeared in the journal *Progress in Cardiovascular Diseases*. Primarily, the papers are clinically oriented and represent a very good survey of the problem of coronary arteriosclerosis and ischemic heart disease. The problems discussed are concerned mainly with diagnosis and treatment. The approach is from the viewpoint of the internist and cardiologist. Among the subjects discussed are acute and chronic coronary heart disease, coronary blood flow, changes in serum enzymes produced by myocardial infarction, difficulties in the electrocardiographic diagnosis of myocardial infarction, the partial vector cardiogram as a supplement to the diagnosis of myocardial infarction, coronary angiography, *intractable angina, treatment of cardiogenic shock*, the role of fibrinolysins in the management of lesions of the coronary arteries.

The presentations as a whole are very good and concise. This is a good book which should interest physicians in practice as well as medical students, interns and house officers.

GENERAL PRINCIPLES OF BLOOD TRANSFUSION. Edited by Max M. Strumia, William H. Crosby, John G. Gibson, Tibor J. Greenwalt and Julius R. Krevans. Philadelphia, 1963, J. B. Lippincott Company. 40 pages. Price $2.

Since the introduction of the services of the blood bank in the late nineteen thirties, inestimable benefit to the patient and clinical medicine has followed. To utilize these services, every physician should have something more than a superficial knowledge of blood transfusion. The editors of *General Principles of Blood Transfusion* present this knowledge in an expertly written 39 pages.

Although there is no index, the table of contents is detailed so that the clinician can readily find specific information with ease. And the specific information included will be found to be invaluable in coping with clinical problems involving transfusion. The listed references also reflect the careful editing that make this an excellent monograph.

Announcements

The University of Colorado School of Medicine announces the third Cochems Competition, funds for which were provided in the will of the late Mrs. Jane Nugent Cochems. A prize of $1,500 will be awarded to the author of the best paper in the field of Thrombophlebitis and Basic Vascular Problem.

The competition is open to all persons holding the M.D. degree and entries must be received in triplicate on or before *November 15, 1964*. For income tax reasons, eligibility is limited to those physicians who are subject to U. S. income tax regulations.

The Colorado National Bank of Denver, Trustees under the will of Jane Nugent Cochems, has requested the Dean of the University of Colorado School of Medicine to conduct the competition. The judges appointed by the Dean are Dr. Michael E. DeBakey, Professor and Head of the Department of Surgery, Baylor University College of Medicine, and Dr. Sol Sherry, Professor of Medicine, Washington University School of Medicine, St. Louis. Decisions of the judges are final and they may elect at their discretion not to award the prize.

Papers submitted in the competition may not be published until after the winner has been an-

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Editorial

Physiologic problems in mitral stenosis

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The relationship between the heart and lungs is structurally and functionally very close, a circumstance which, although obvious, seems to have had little influence on clinical knowledge and practice until comparatively recently. Cardiologists have not in general concerned themselves with the complexities of pulmonary function in health and disease, and chest physicians have not until recently taken an interest in cardiology. The chief reason for this unfortunate dichotomy has been the dominant influence of tuberculosis in chest medicine. The fact that this disease is infectious has led to the intellectual as well as physical isolation of disordered lung function. It is well nigh impossible to specialize in a scientific sense in pure cardiology as opposed to pure chest diseases. Useful investigation and competent clinical practice demand their fusion.

Such a unity of outlook is one of the guiding principles of the Department of Medicine of the Birmingham (England) Medical School. Their studies of the lungs in mitral stenosis during the last 17 years have been reviewed recently. These studies cover a number of effects of mitral valve disease on pulmonary function.

Damage to the mitral valve is the principal factor that causes the disability from chronic rheumatic heart disease. Apart from disturbances of rhythm, such as atrial fibrillation, there is little evidence that the myocardium as a contractile machine is impaired. Indeed, there is ample evidence of its high efficiency in the way it maintains over many years a much augmented load with little tendency to sudden arrest or ventricular fibrillation. The cardiac failure which eventually supervenes is due either to atrial fibrillation or—and this is more important—to the fact that the contractile power of the right ventricle, powerful as it is, cannot force an adequate amount of blood through the pulmonary circulation and on through the narrowed mitral valve.

It is not surprising that the abnormalities of mitral stenosis are referable not only to the pulmonary circulation but to the whole function and structure of the lungs. If one approached the syndrome of mitral stenosis with reference to the abnormal shape, the disordered rhythm, and the characteristic noises of the heart, one would regard the whole condition as a pulmonary disorder. The patient's chief complaint is shortness of breath, particularly on exercise. There are a whole range of disordered

From the [illegible] of Birmingham, Birmingham, England.
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respiratory mechanisms and the most striking effect of the operation of valvotomy is to reduce the magnitude of these respiratory abnormalities. Furthermore there are important structural changes in the lung which carry great physiologic significance and which influence treatment.

A study[4] of the cardiac output in 193 patients with pure mitral stenosis showed that the mean resting cardiac index of 2.73 L per minute per square meter of body surface is at the lower end of the range reported for normal subjects. Low values were more numerous in those with greater disability, although the association was not close. The patients with atrial fibrillation had a markedly low cardiac index (2.31 L.) as compared with a value of 3.02 L. for those in sinus rhythm. Pulmonary arterial pressures were elevated in all but the mildest cases. Pulmonary hypertension was present in the artery, the pulmonary capillaries and left atrium as gauged by the wedge pressures. There was a close correlation between the degree of pulmonary hypertension and disability. Studies of pulmonary hemodynamics during exercise showed striking elevations in pulmonary pressures and a marked inability to increase cardiac output, the increased oxygen transport being secured by a high tissue coefficient of oxygen utilization.

The studies yielded ample evidence of the well known phenomenon that, whereas there is a roughly rectilinear relationship between pulmonary arterial pressure and pulmonary wedge pressure up to resting values of approximately 25 mm. Hg, thereafter the resting pulmonary wedge pressure rises only very slowly, although pulmonary arterial pressure may go on rising up to levels which approach those of systemic arterial pressure. This points conclusively to the development of a pressure gradient between the pulmonary artery and the pulmonary capillaries. There is ample histologic evidence of this, especially in the studies of Harris and Heath.[5] This takes the form of the development of a muscular coat in the small pulmonary arteries (<1,000μ) and the pulmonary arterioles. This is followed by subintimal thickening. These vessels therefore become actively contractile tubes narrowed somewhat by thickening of the intimal and middle coats. The principal stimulus to contraction is probably the surges of bursting force which result from a powerfully acting right ventricle and a stenosed mitral valve. It is perhaps not a bad thing that this precapillary impedance develops since, although it certainly imposes additional work on the right ventricle, it protects the pulmonary capillaries from pressure levels which would produce severe pulmonary edema. Indeed minor degrees of edema must be common in mitral stenosis, especially during exercise. Some of the fluid which escapes into the connective tissue planes and alveoli contains protein and is capable of inciting some degree of inflammatory response characterized by the laying down of new connective tissue. Eppinger[6] elaborated this theme and referred to albuminuria into the tissue. The frequency with which severe pulmonary edema occurs in young pregnant women with mitral stenosis may well be due to the fact that this precapillary impedance has not yet developed at a time when the pulmonary pressures are quickly elevated by the increased cardiac output and hypervolemia of pregnancy. In mitral stenosis, therefore, the lungs are subjected over the years to raised pulmonary venous pressure with, in consequence, a progressive elevation in pressures back to the right ventricle and the development of changes in the walls of the vessels. As the condition advances, the lungs are subject to an increasing number of attacks of edema with the escape of fluid and sometimes red cells not only into the alveolar spaces but also into the walls of vessels, alveolar septa and pleural layers—indeed throughout the entire structure of the lung. The result of this is the gradual coarsening of the lung tissue so that it becomes stiffer and heavier. These changes have effects on all aspects of pulmonary function.

The static divisions of lung volume show a somewhat complex pattern of changes, prominent among which is reduction in vital capacity.[7]

Dynamic changes are of greater importance. The ventilatory work of breathing is of two main types, one directed to overcoming the elastic recoil of the lungs and the other concerned with the movement of air through the respiratory pas-

sages The former aspect is a function of the properties of the lung tissues that is their stiffness (or compliance) whereas the latter is determined principally by the caliber of the air passages and the amount of turbulence determined by their configuration White Butler and Donald in the Birmingham laboratories investigated the relationship between hemodynamic changes and lung compliance in patients with mitral disease The value of the compliance showed a progressive diminution with increasing disability that is there was a close inverse correlation between compliance and pulmonary arterial pressure and particularly the wedge pressure

Marshall McIlroy and Christie[8] calculated the total work done in pulmonary ventilation by patients with mitral stenosis during both rest and exercise and found that they had to do about 2 to 3 times as much work as normal people in order to achieve a given minute volume

It is not surprising that the process of lung stiffening should interfere with the distribution of air Raine and Bishop[9] studied 20 patients with mitral stenosis matched with 20 normal people Distribution of air of a single maximum breath of oxygen was measured by the nitrogen meter and was found to be defective in patients with mitral stenosis and became increasingly so during exercise It was postulated that this was due to increased transudation of fluid from the pulmonary capillaries into the lungs as the result of pulmonary venous hypertension Careful controls were carried out to ensure that these changes were not due simply to chronic bronchitis

One of the most vital aspects of pulmonary function is the ventilation perfusion relationship Respiratory effort must ensure the absorption of the requisite amount of oxygen and the excretion of a somewhat smaller amount of carbon dioxide Although this effort is the resultant of the function of all the alveoli in each individual alveolus the amount of exchange is determined by the gas gradients which depend on a critical relationship between the amount of blood passing through the capillaries and the amount of air passing in and out of the alveolus Whereas not all alveoli are functioning at the same level the statistical profile of their function must satisfy the overall demands set by the metabolic exchange ratio There seems to exist in the lungs a local mechanism which adjusts alveolar blood flow to ventilatory level A reduction in oxygen tension constricts blood vessels thereby reducing the perfusion in parallel with the reduction in ventilation

In a series of studies the Birmingham group[10,11] has studied blood gas distribution using a variety of experimental devices such as the breathing of oxygen at 21 47 and 100 per cent and the action of acetylcholine which exercised a differentially greater effect on constricted vessels The results of these studies support conclusively the existence in mitral stenosis of substantial abnormalities of ventilation/perfusion relationships In view of these changes in function and structure that occur in the lungs as the result of mitral stenosis it is not surprising that increased ventilation and its subjective component of dyspnea are the most prominent clinical features of chronic rheumatic heart disease

Donald Bishop and Wade studied the minute to minute changes in ventilation oxygen uptake arteriovenous oxygen difference and cardiac output during exercise in 16 patients all of whom had mitral stenosis The results can be summarized by stating that as the grade of disability increased the ventilatory volume during rest and exercise increased and the amount of oxygen extracted per unit of ventilation diminished progressively

The important question arises whether ventilation in mitral stenosis is adequate The results of these and many other studies suggest that it is on the whole adequate if one takes as criteria the maintenance of arterial oxygen and carbon dioxide tensions at physiologic levels in fact it may be even excessive in that there is hyperventilation to the extent of depressing the PCO to levels approaching 30 mm Hg On the other hand if the question is posed whether ventilation is efficient in mitral stenosis the answer is undoubtedly no It costs too much in terms of the most basic currency in nature that is energy expressed as oxygen consumed

It is known that the reduced cardiac

output and increased arteriovenous oxygen difference exposes the various regions of the body to greatly reduced mean oxygen tensions in their blood supply. A series of reports by the Birmingham group on abnormal patterns of regional blood flow at rest and during exercise in mitral stenosis has been reviewed by Donald.[13] One fact emerges clearly and that is the remarkable degree of preservation of cerebral blood flow in the face of severe restriction of cardiac output. Particularly striking is the reduction in splanchnic blood flow as well as the reduction in blood flow in resting muscles during exercise of other muscle groups. During exercise in some patients with mitral stenosis some territories may have their blood supply so reduced that the venous blood leaves its capillaries almost completely stripped of oxygen.

Studies[14,15] of the physiologic effects of mitral valvotomy show, apart from the increased efficiency and well being of the patients, that the most striking measurable change is the reduction in resting and exercise ventilation, thus the improvement is essentially in respiratory function. The pattern of cardiac output shows little change, and pulmonary arterial and wedge pressures show considerable reduction at rest although not to normal levels. There was a striking correlation between resting ventilation and wedge pressure before and after operation. It seems quite likely that the reduction in pulmonary vascular pressure has an ameliorating influence on pulmonary turgidity and thus on ventilatory effort.

These studies and many others of a similar nature in other laboratories point to pulmonary hypertension and its effects on lung function and structure as the principal harmful effect of mitral stenosis. The lesson to be learned therefore by clinicians is that in mitral stenosis once there is clear evidence (by catheterization) of pulmonary hypertension mitral valvotomy should be performed.

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Clinical communications

A portable pump for the protracted injection of parenteral fluids

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Our development of a multichannel radio telemetering instrument for recording ambulant physiologic signals necessitated the construction of a small portable pump for injecting controlled amounts of an anticoagulant into an indwelling arterial catheter.[1] It follows that such a pump would have sundry clinical uses, provided that it had simplicity of operation and dependability in the hands of both physicians and paramedical personnel. This communication includes the design, description, testing, and uses of such a pump.

A number of designs were constructed and tested. The model adopted is illustrated in Figs. 1 and 2 and consists of a small precision DC motor with a current drain of about 35 milliamperes, an integral gear train that is part of the motor enclosure, and a DeBakey type pump. This assembly weighs 115 grams. The pump unit includes 5 Teflon rollers on the rotor and clearances are set so that the pump is occlusive when the tubing walls are pressed together. The pump will develop pressures of 20 to 25 pounds per square inch and a vacuum of 10 to 12 pounds.

The speed of injection is controlled by the voltage of the motor, the gear ratio, and the size of the plastic tubing used. The speed of injection is proportional to the voltage over a range of 4 to 12 volts. If the speed is held constant, numerous tests have shown that the rate of injection can be held constant to 1 or 2 per cent over periods up to 1 week. This accuracy is rarely needed in our present experience and usually an accuracy of 5 to 10 per cent variation is adequate.

The choice of power supply depends upon (1) the accuracy of injection desired and (2) whether ambulant or bedside injection is desired. Dry batteries show a fairly steady drop in voltage with time and for this reason provide generally the least accurate rates of injection. Generally, the loss in speed of injection would not be greater than 10 per cent during an 8 hour period. They have the advantage of being stock items in the central supply room and do not require recharging, etc. Nickel cadmium rechargeable batteries are adequate for 8 hours of injection, after which they need recharging. The drop in voltage with time is definitely less than with the dry battery. A rectifier power supply is excellent but does not permit ambulation. In many cases we have used

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Table I

Catheter length	Pump tube length (cm)	Resonant frequency — ω (cps)	Damping ratio $\left(\frac{C}{C_c}\right)$
2 N 20 Needle	00	135	0 101
30 in No 6	00	54 2	0 119
90 in N 6	00	47 5	0 123
90 in No 6	20	37 8	0 205
90 in N 6	40	42 5	0 185
90 in No 6	30	40 1	0 166
90 in N 6	50	40 1	0 166
90 in No 6	60	40 6	0 198
90 in No 6	80	47 4	0 172

Diam [illegible] of pump tube was 0 011 inch I D (Tygon tubing)

nickel cadmium batteries when the patient wanted to move around If the patient was in bed or sitting down he disconnected the motor cord and plugged it into the rectifier unit Most commonly we have used a model 721 A Hewlett Packard Power Supply

At present each pump unit uses tubing of only one outside diameter Other rates of injection require a change in gear ratio or tubing diameter We are developing interchangeable groove and pressure plates to permit the use of different sizes of tubing and also outside plastic sleeves to permit the use of tubes with smaller inside diameters Present models in use include rates of injection from 0 4 to 300 c c per hour

Silastic tubing formula 372 works well and we have had continuous injections of over a week and have never found any damage to the tubing

In the earlier work we used a Tygon formula which has physical properties closely resembling Silastic 372 A particular advantage is that Silastic 372 will not creep in the pump so that we have been able to simplify pump design Both tubings can be sterilized in the autoclave The Statham gauges require cold sterilization and we followed the manufacturer's directions and used Zephiran solution Zephiran was also used for the catheters according to the manufacturer's specifications There were no difficulties with infection

In order to demonstrate the fidelity of recording the natural resonant frequency and the damping ratio were determined for various lengths of catheter and of pump tubing The data are recorded in Table I For example line 1 shows that with a steel needle directly connected to the Statham gauge and no pump tubing the resonant frequency is 135 c p s and the damping ratio is 0 101 The addition of catheter lengths and Tygon pump tubing lowers the resonant frequency but the system is quite adequate for the detailed recording of blood pressure

The resonant frequency and damping ratio measurements were done as follows After assembling each combination of needle catheter length pump tubing and Statham gauge a step function was applied The system was filled carefully with water containing a small amount of detergent to assist in the elimination of bubbles A finger cot was attached to the system This was filled with air to a pressure of usually 130 mm Hg The sudden release of pressure by rupturing the finger cot was the step function This was done with a razor blade During the cutting procedure relays started the sweep of the Tektronix 502 and opened the shutter of the Polaroid camera The photographed record consisted of the diminishing vibrations of the pressure gauge and a time base

If successive amplitudes in the same direction are measured as X_1 X_{1+r} then $\delta = L\left(\frac{X_1}{X_{1+r}}\right)$ when δ is the logarithmic decrement

The damping ratio

$$\frac{C}{C_c} \text{ is } \frac{C}{C_c} = \frac{\delta}{\sqrt{\delta^2 + 4\pi^2}}$$

ω_d the frequency of the damped waves is measured on the photos and with the formula $\frac{\omega_d}{\omega} = \sqrt{1 - \left(\frac{C}{C_c}\right)^2}$ ω the natural resonant frequency is determined[4,5]

The pump as illustrated has been in use for over 2 years and has been well accepted by physicians and paramedical personnel It has been used for (1) anticoagulant flushing of the arterial system in ambulant blood pressure studies monitoring in heart surgery and postoperative

tively (2) exterior heparinization and addition of protamine in blood dialysis therapy (3) injections of Nembutal anesthesia in mice (4) intravenous injections of fluid chemotherapeutic agents for cancer and reinjection of ascitic fluid (5) food ingestion at rates of 1 c c per minute (1 c c = 1 calorie) over continuous periods of a week (6) pressure dialysis and filtration of ascitic fluid for reinjection

In practice the pump has proved to be easy to use Most DeBakey pumps require a clamping or holding device to prevent creeping of the tubing by the rollers The

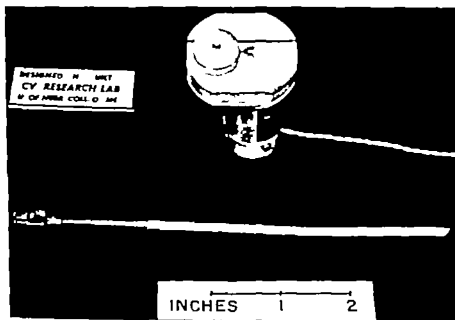


Fig 1 Motor and pump

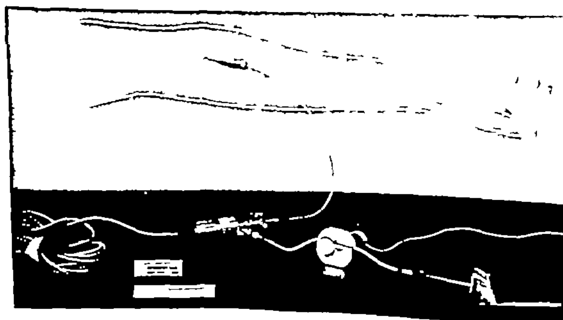


Fig 2 Pump assembly for arterial

Silastic tubing which we use does not creep when a properly designed groove is used. This simplifies applying and removing the tubing from the pump. We use plastic bags for holding the fluid and remove all air from the bag. This prevents the injection of air. We had planned various holders for supporting the pump but find that adhesive tape is much preferred. Recent tapes are not gummy and permit attachment where desired.

Summary

A small portable electric motor and De Bakey type pump which weighs 115 grams has been constructed and tested. Rates of injection of 0.4 to 300 c.c. per hour with voltage control can be maintained for periods of over a week within a few per cent. The pump can be operated as a portable unit with batteries or at the bedside with a DC rectifier from the 115 volt AC lines.

The step function studies were done by Roland Rader and Alfred Kurtenbach, M.S. students in the joint Bio-Medical Engineering Program of the University of Nebraska Department of Engineering and College of Medicine.

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Some hemodynamic aspects of cardiac arrhythmias in man

A clinico-physiologic correlation

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Patients describe a wide variety of peculiar symptoms in association with cardiac arrhythmias and it is the purpose of this paper, which presents a collection of hemodynamic data in such states, to uncover any possible clinical counterparts of disturbed hemodynamic functions. The pressure curves were recorded during cardiac catheterization and, when available, cardiac output was determined according to the Fick principle. Some of the data have been published previously.[1-4] The presentation will be divided into two sections: hemodynamic findings in the *intermittent arrhythmias* and those seen in the *more permanent or fixed arrhythmias*.

Intermittent arrhythmias

Sinus arrhythmia. There is one point of interest in regard to this relatively unimportant arrhythmia—namely, that it can result in the production of false pulsus alternans as seen in Fig. 1. As a consequence of the influence of respiration on the one hand and cycle length or filling time on the other, alternation of pressure is produced which has no clinical significance. Hence cautionary comment on the diagnosis of alternation of systemic blood pressure in the presence of sinus arrhythmia is warranted.

Premature contractions

ALTERNATION. Atrial premature contractions (APC) can also produce false pulsus alternans, as can be seen in Fig. 2. True alternans, on the other hand, can be initiated in the diseased heart by a single atrial premature contraction. In Fig. 3 one notes the initiation of bilateral alternans after only one premature atrial contraction. Alternans in the brachial artery ceases after the fourth postextrasystolic beat, although alternation persists for 10 beats in the pulmonary artery, as shown between the arrows, suggesting more disturbance in right than in left ventricular function. It is well known that the appearance of variations in size of pulse beats after a premature contraction can persist for two or three beats after the premature systole on the basis of readjustments in stroke volume. Such adjustments would not go on for as long as 10 beats and also would not explain the per-

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Fig 1 False alternans during sinus arrhythmia Note that the pulmonary artery (*PA*) shows the alternating size of the pulse waves more clearly than the brachial artery (*BA*) below it The level of diastolic pressure in both arteries varies directly with the respiratory cycle as is the case normally and reaches its peak at full inspiration The pulse pressure of these beats however is related to long and short cycle times as well as to respiratory variations The second and third pulmonary artery beats have the same cycle lengths but occur during the inspiratory phase hence the second exceeds the first in height whereas the third is waning The fourth beat however occurs after a longer diastole and although on the basis of the respiratory pattern it should be declining it is larger because of a longer filling time a greater diastolic volume and presumably a larger stroke volume The fifth beat should be the smallest owing to the respiratory influence but having the longest diastole of all and hence the largest stroke output it achieves the same size as the fourth beat The sixth beat with short diastole occurs at the end of expiration and is again a small one whereas with inspiration the seventh beat grows larger despite a short filling period (From Ferrer et al *Circulation* 14 163 1956 by *permission of the American Heart Association Inc*)

sistence of alternans in the pulmonary artery when it had ceased in the brachial artery

TRICUSPID AND MITRAL REGURGITATION The relationship of the atrial and ventricular mechanical events during premature contractions are of particular interest with regard to the production of tricuspid and mitral regurgitation It is well known that the occurrence of an atrial contraction before the onset of ventricular systole is essential to efficient closure of these valves This was shown for the tricuspid valve by Little[6,7] and Grant[8] and for the mitral valve by Sarnoff[9,10] and Brockman[11] without it they become insufficient The atrial systolic augmentation of ventricular tension and hence stroke output has also recently been recognized[10] thus implying a lower stroke output in the absence of atrial systole Fig 4 taken from Sir Thomas Lewis illustrates the three venous pressure curves of insufficiency (numbered *2 3 4*) compared to a normal curve (number *1*) These jugular vein curves are virtually identical to right atrial curves The validity of these pressure contours as evidence for regurgitation has been shown by Sarnoff[10] who used a hydrogen electrode sensitive to injections of ascorbic acid and demonstrated the reflux of acid into the left atrium during mitral insufficiency characterized by these curves This insufficiency was produced by improper timing of atrial systole in relation to the ventricular event Sarnoff[10] has even defined the optimal A V interval in dogs and found that regurgitation occurs outside the range of 60 to 120 msec

When an atrial premature contraction (APC) occurs the atrial pressure curve may resemble that produced by a sinus beat (as was seen in Fig 2) However if the APC is quite premature there will be some variation in atrial pressure as seen in Fig 5 The first and third atrial premature beats (APC_1 and APC_3) produce large atrial contractions because they occur when the tricuspid valve is still closed By contrast in the second and fourth premature beats (APC_2 and APC_4) the valve has opened and the atrial pressure contour is not unusual The variations in atrial systolic pressure can be great enough to be felt by the patient especially in the jugular pulse and neck region and produce the symptoms of pulsations or fullness or throbbing in the neck perhaps a lump in the throat In this same Fig 5 compare the two ventricular premature contractions (*VPC*) One occurs after the sinus P wave and hence after an atrial contraction (*A* in the pressure curve) and produces a nearly normal atrial pulse contour whereas the other occurring before the P wave and hence not preceded by an atrial systole initiates a ventricular contraction accompanied by pressure evidence of tricuspid insufficiency

Tricuspid regurgitation is apparently reflected easily into the hepatic vein as can be seen in Fig 6 There are four ventricular premature contractions in this

tracing and only the third is preceded by a P wave and hence an atrial systole. In this third beat the tricuspid valve remains competent but regurgitation occurs with each of the other 3 VPCs although there was neither atrial nor hepatic venous hypertension. The hepatic venous trace is marked with arrows when there is regurgitation. The regurgitant beats in the liver could conceivably be linked to transient abdominal symptoms especially those related to the splanchnic bed. It is also of interest to note how much smaller are the brachial arterial pressures resulting from those VPCs associated with tricuspid insufficiency (*T I*) than the one beat resulting from a VPC without it. There is some but not a large difference in the degree of prematurity of these beats but this is probably not entirely responsible for the difference in pressures. There may also be a loss of volume from the ventricles into the atria because of A V valve insufficiency which contributes along with the shortened filling time to depleting the stroke output into the aorta and pulmonary artery. The effect of regurgitation in diminishing stroke output may clarify some of the hitherto unexplained variations in arterial pulse pressure with ventricular premature contractions i e those beats with T I have smaller curves than those beats without it. The postextrasystolic beat may also vary in size depending upon the quantity of the regurgitated volume which immediately returns to the ventricle as well as upon the length of the ventricular filling time.

The effects of regurgitation may extend well beyond the inferior vena cava and

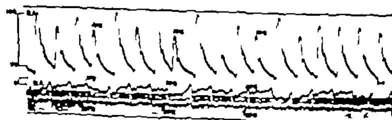


Fig 2 False alternans in brachial artery due to atrial premature contractions. Note the usual small beat in the brachial artery after the premature excitation, the larger postextrasystolic beat, and the smaller beat that follows the latter. The timing of the premature atrial contractions is such that because of variation in diastolic filling and ventricular emptying a continuous alternation in the brachial artery occurs until the last five beats in the figure where normal sinus rhythm appears uninterrupted by atrial premature systoles. The atrial curve (*RA*) shows a relatively normal mechanical atrial event for each premature beat (*APC*) and there is no alternation in atrial pressure or evidence of tricuspid insufficiency. (From Ferrer et al, Circulation 14 163 1956 by permission of the American Heart Association Inc.)

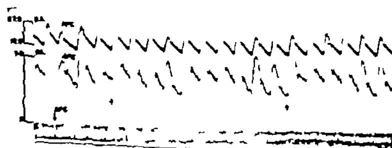


Fig 3 Pulsus alternans after an atrial premature contraction. For discussion see text. (From Ferrer et al, *Circulation 14 1 3 1956* by permission of the American Heart Association Inc.)

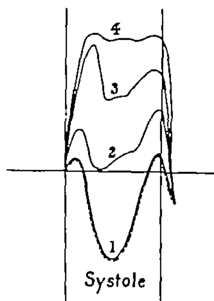


Fig. 4. Three examples taken from Sir Thomas Lewis of jugular vein pressure curves in valvular (tricuspid) insufficiency (marked *2, 3, 4*) as contrasted to a normal jugular venous pressure curve (*in dotted line*). The space between vertical lines marks ventricular systole. Note that in the curves depicting insufficiency the pressure rises early during ventricular systole and never falls below the base line as it does with a competent tricuspid valve. (Reproduced from Sir Thomas Lewis: *The Mechanism and Graphic Registration of the Heart Beat*, ed. 3, London, 1925, by permission of Shaw and Sons, Ltd.)

hepatic vein into other venous beds (renal, etc.) and hence the volume lost in regurgitation may not instantly return to the atria and if sequestered in other organs as well may result in a temporary fall in cardiac output. If this fall is significant and sustained for any appreciable period of time, symptoms of fatigue or dizziness may follow.

A central A-V nodal premature contraction (Fig. 7) is also associated with a large pulse wave in the atria when the P wave and consequently atrial systole do not precede but occur simultaneously with the QRS and ventricular systole, respectively. It is not possible at present to determine from this pressure curve alone whether the large pulsation is due to atrial systole operating against a closed tricuspid valve or tricuspid insufficiency. The existence of the latter possibility appears to be more likely in view of Sarnoff's work on optimal A-V intervals as mentioned above.[19] Such atrial and hence jugular pulses, however, may well produce unusual sensations in the throat or upper thorax.

It might be thought that heart failure and a high atrial pressure should often or even always produce tricuspid or mitral insufficiency due to a dilated annulus. Actually this is not so. The patient from whom the curves shown in Fig. 8 were obtained had severe right heart failure with elevated right atrial pressure and yet no evidence of tricuspid insufficiency (T.I.) accompanied the sinus beats (compare the curve with the normal right atrial curve below it). Tricuspid insufficiency did appear with the VPCs since P waves

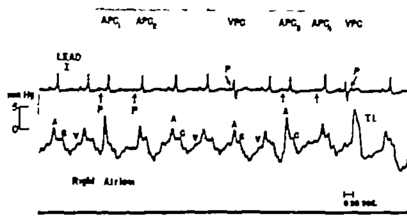


Fig. 5. Right atrial pressure curve and Lead I showing multiple atrial premature contractions (*APC*) and two ventricular premature contractions (*VPC*). For discussion see text.

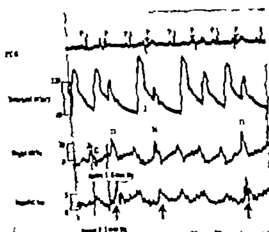


Fig 6 The appearance of tricuspid insufficiency produced by VPCs as seen in the right atrial curve and as reflected also into the hepatic venous bed Normal sinus rhythm with normal atrial excitation (P waves) permits undisturbed by the VPCs For discussion see text

do not appear before these VPCs hence the protective presence of an atrial systole before the ventricular systole was missed The wide atrial pressure oscillations in this patient in failure produced a pulsating liver with every beat although there was no evidence of tricuspid insufficiency with these sinus beats In a number of other patients with right heart failure whom we studied namely those with cor pulmonale this same freedom from tricuspid regurgitation was a consistent finding Similarly a patient with the lowest cardiac output recorded in our laboratory a cardiac index of 0 99 displayed no evidence of tricuspid regurgitation even though he was in marked right and left failure with sinus rhythm and later died of a ventricular aneurysm due to coronary artery disease

VENTRICULAR ASYNCHRONISM Turning now to bigeminal rhythm due to coupled ventricular premature contractions (VPCs) we see in Fig 9 an interesting example of ventricular asynchronism The coupled VPC produces too small a left ventricular contraction to open the aortic valve (the left ventricle does not eject and there is no brachial pulse wave) and yet the right ventricular contraction and stroke output are enough to open the pulmonic valve (the right ventricle does eject and produce a small but definite pulmonary arterial pulse) Surely such an abnormal function one ventricle ejecting while the other does not produces some pulmonary vascular congestion and can account for some of the weird sensations (e g such a breathlessness chest fullness or a bursting feeling) complained of by those experiencing VPCs with coupling In Fig 10 there are VPCs occurring irregularly and erratically which so vary the stroke output that as they become more frequent they increase the right ventricular diastolic

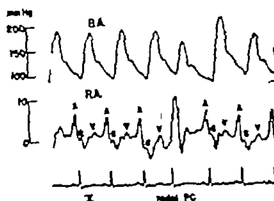


Fig 7 Tricuspid insufficiency produced by a single central A V nodal premature contraction (I wave fall during QRS) occurring during normal sinus rhythm R A Right atrial curve B A Brachial artery curve Electrocardiographic Lead II

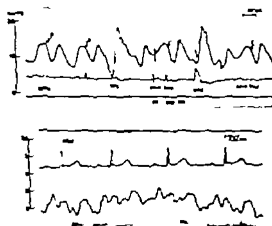


Fig 8 Right atrial curves in right heart failure with atrial hypertension (upper) and curves with normal pressure values (lower) A = atrial systole C = ventricular contraction I = filling point of right atrium just before the tricuspid valve opens Note the tricuspid insufficiency occurring only with VPCs as I waves do not precede QRS in those beats For discussion see text



Fig 9 Brachial (B A) and pulmonary artery (P A) curves demonstrating the effect of the onset of coupled VCP For discussion see text



Fig 10 Brachial artery (B A) and right ventricular (R V) curves demonstrating the effect of numerous VPCs occurring erratically during sinus rhythm For discussion see text

pressure to abnormal levels for this brief period (see the fifth and sixth VPCs in the center of the figure) Thus left heart failure which was present before the VPCs began as evidenced by the elevated right ventricular systolic pressure was complicated by stress of the right ventricle as well Such stressful episodes may also act to effect the retention of sodium and water and increase blood volume [1]

Paroxysmal ventricular tachycardia (V T) Spontaneous bursts of ventricular tachycardia are seldom recorded during cardiac catheterization but Fig 11 is one such instance It was not related to maneuvering of the catheter which had been in place for some time Note that during these short runs of ventricular tachycardia with a rate equivalent to 250 there is no ejection of the left ventricle since there is no brachial artery pulse (upper trace) presumably there was also no flow of blood to any part of the systemic circulation The right atrial pressure rises during this time as the atrial systoles continue in response to the basic rhythm of atrial flutter The lower trace presents the right ventricular (R V) curve as well as the peripheral artery curve The ventricular beats during V T (numbered) are very small and some probably do not open the pulmonic valve in addition the ventricular diastolic and hence peripheral venous pressure both rise with each bout of this arrhythmia These bouts of arrhythmia certainly could produce symptoms in the central nervous system and splanchnic bed even if only of short duration

Permanent or fixed arrhythmias

A V nodal tachycardia Two patients with the Wolff Parkinson White syndrome and episodes of this rhythm characterized by a *retrograde P wave after the QRS were* available for study in and out of tachycardia During the tachycardia (with a rate of 187) there was a marked alteration in pressures (a large upward unidirectional curve) in the right atrium superior vena cava and to a much lesser degree the subclavian vein (Fig 12 and Table I) as compared with the normal tracings The contours of the abnormal pressure curves in the atrium during nodal tachy

cardia are identical to those in the jugular tracings described by Sir Thomas Lewis who considered them to be combination A and C waves The curves in the superior vena cava resemble those in the right atrium very closely and presumably the inferior caval curves would do so too Jugular vein tracings would no doubt approximate those in the superior vena cava since there is no valve between these two venous channels There is a striking difference however in the tracings taken in the subclavian vein largely because a competent venous valve separates this vein from the innominate This is evidenced also by the large difference in pressure between the superior vena cava and the subclavian vein In spite of the dampening effect of this valve on the regurgitant pulse wave as it travels backward through the large intrathoracic veins a sharp rise in pressure appears which corresponds to the rise in pressure in the right atrium thus permitting the suggestion of chest symptoms in the subclavian area on this basis

Comparison of the mean pressures in the right atrium during sinus rhythm and accelerated A V conduction of the Wolff Parkinson White type and nodal tachycardia (Table I) demonstrates the considerable increase in pressure (fourfold to sixfold) during tachycardia During sinus rhythm the right atrial mean pressure was 2 0 mm Hg (27 mm of water) and during nodal tachycardia the mean pressure rose to 8 0 mm Hg (109 mm of water) The peaks of rise in atrial pressure actually reached 20 mm Hg (272 mm of water) whereas normal atrial systole rarely exceeds

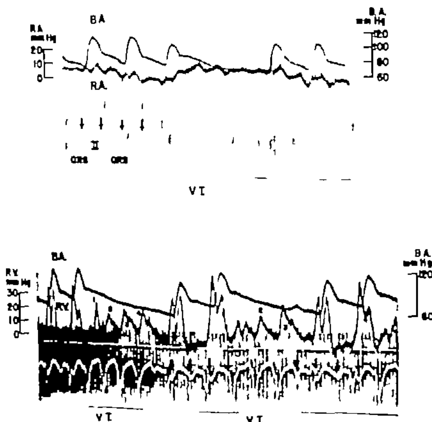


Fig 11 Brachial artery (B A) right atrial (R A) (*upper frame*) and right ventricular (R V) (*lower frame*) curves recorded during short bouts of paroxysmal ventricular tachycardia occurring during atrial flutter (flutter waves are marked with arrows) For discussion see text

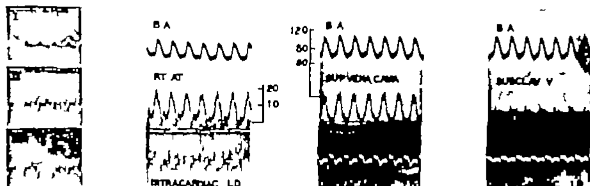


Fig. 12 Curves from the brachial artery (*B A*), right atrium (*Rt At*), superior vena cava, and subclavian vein depicting the effect of A V nodal tachycardia. The three standard ECG leads are to the left. The intracardiac electrode was incorporated into the catheter and ECG traces under the pressure curves are therefore taken from the latter three cardiac sites.

5 mm Hg (68 mm of water). This peak rise in pressure approaches the normal right ventricular systolic pressure level. This abnormal rise in pressure in the right atrium is probably due to the summation of two events: (1) regurgitation of blood through the tricuspid valve during ventricular isometric contraction and early ejection and (2) atrial systolic contraction after the retrograde P wave. The occurrence of both events in rapid succession would be inscribed as a single upward deflection of marked amplitude. The cause of the tricuspid regurgitation is the absence of the occurrence of a normal atrial systole before ventricular contraction,[4,11] since P wave and atrial systole follow the ventricular event. The resultant very high peak of atrial pressure in this rhythm probably favors unimpeded retrograde flow back into the intrathoracic venous system as far as the first peripheral venous valves during part of the cardiac cycle. Thus atrial filling which normally takes place during ventricular systole is impeded and inadequate because of this retrograde flow as well as the abnormally high atrial pressures. The filling of the atria is limited therefore to the very short interval during which the atrial pressure is falling and the filling of the ventricles is probably reduced during the short period of diastolic inflow.

With such disturbances in blood flow it is not surprising that during this form of A V nodal tachycardia the cardiac output is not greater than during normal sinus rhythm in these two noncardiac subjects (Table I) and that stroke volume is considerably reduced. By contrast it is well known that there is usually an increase in cardiac output with episodes of sinus tachycardia.[12,13]

Further information concerning tricuspid regurgitation in A V nodal tachycardia with retrograde P waves is found in Fig. 13 (taken from a third subject with Wolff-Parkinson-White syndrome) which reveals the offset of this abnormal rhythm with conversion to normal sinus rhythm. The regurgitant characteristics are seen in the superior vena caval curve during the nodal rhythm and are lost as soon as the sinus mechanism supervenes. The pressure curve from the right atrium was virtually identical with that from the superior vena cava when subsequently compared. However, it is especially pertinent to the consideration of disturbances in flow and to possible symptoms to note that the elevated mean caval pressure determined during the tachycardia does not fall to normal (from 9 to 1 mm Hg) until 4 minutes after restoration to sinus rhythm, which confirms the previous statement that the disturbance in volume (and perhaps also the disturbances in flow) imposed by tricuspid insufficiency may persist for some period after the valve again becomes competent. The systemic arterial pressure curve also changes markedly immediately after conversion, but 4 minutes later it is still abnormal—142/104 mm Hg with a mean of 119. Thus it is apparent at least

in the normal heart that the immediate adjustments which occur in this arrhythmia do not disappear instantly after cessation of the tachycardia. On the other hand they may not be very long lived and may disappear after a few beats or at most a few minutes after conversion to sinus mechanism.

Tricuspid regurgitation also occurs in almost every beat during an example of *A-V dissociation with interference and His bundle rhythm* (Fig. 14). In this situation the independent ventricular beats (originating in the bundle of His) which occur at a faster rate (88 per minute) than the atrial contractions (41 to 45 per minute with sinus arrhythmia) begin for the most part without a preceding atrial systole. Only when by chance P waves precede the QRS is the right atrial curve of normal contour. This occurs twice in this Fig. 14.

Atrial flutter and atrial fibrillation. Although these two arrhythmias have a close relationship clinically and one often merges into the other, there are certain distinct dissimilarities between them.

In the first place, in *atrial flutter* each electrical flutter wave elicits a mechanical atrial systole regardless of the speed of the atrial rhythm. In a report from this laboratory [4] flutter waves productive of atrial systole between 230 and 340 per minute were demonstrated. These atrial contractions are present not only throughout the right atrial and right ventricular curves but also surprisingly in pulmonary arterial and brachial arterial curves as well. One must assume in the latter two locations that impacts produced by the *left* atrial systoles are responsible and are transmitted directly to the walls of both great vessels. By contrast, in atrial fibrillation individual discrete atrial systoles are not seen anywhere.

Another point of difference between these two atrial mechanisms is the very frequent, indeed almost invariable, presence of tricuspid (and probably also mitral) insufficiency in atrial fibrillation, even in the absence of elevated right atrial pressure or heart failure, whereas insufficiency rarely if ever occurs in atrial flutter. This distinction is further emphasized when one notes that in the atrial rhythm designated

Table I. Hemodynamic data in 2 patients with Wolff-Parkinson-White syndrome and paroxysmal A-V nodal tachycardia

Patient	Pulse rate	Blood pressures (mm. Hg): Brachial artery (Systolic/Diastolic)	Blood pressures (mm. Hg): Brachial artery Mean	Blood pressures (mm. Hg): Right ventricle (Systolic/Diastolic)	Blood pressures (mm. Hg): Right atrium (Mean)	Cardiac output: c.c./min./M.²	Cardiac output: Per beat	Peripheral resistance (dynes cm.⁻⁵ sec.)
Normal		120/70	85	30/2	3 to −3	3.12 ± 0.4	50–90	1,500
G. F.								
Nodal tachycardia	187	102/73	80	—	+7.8	3.39	27	1,130
WPW conduction with right bundle of Kent	78	104/66	77	28/3	+1.5	3.16	60	1,240
K. Y.								
Nodal tachycardia	178	105/77	90	—	+5.8	2.30	24	1,600
WPW conduction with left bundle of Kent	121	104/77	84	32/1	+0.5	2.79	34	1,590

For discussion, see text.

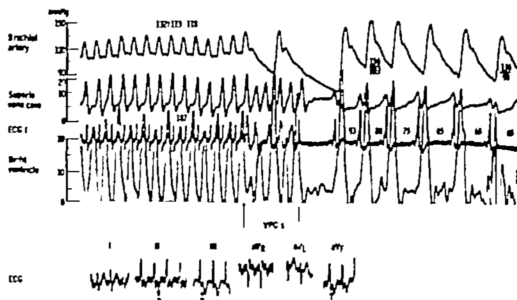


Fig. 13. Curves from the brachial artery, superior vena cava, and right ventricle during A-V nodal tachycardia at 187 per minute, *showing the grossly distorted caval curve, small arterial pulse pressure*, and bilateral (*B. A.* and *R. V.*) pulsus alternans. (The six limb leads of the ECG are seen at the bottom to indicate the retrograde P wave.) After conversion to sinus rhythm (following a group of 5 VPCs) accelerated A-V conduction (with short P-R and long QRS) of the Wolff-Parkinson-White type is seen. The initial sinus rate after conversion was 93; this fell to 65 in four beats. The elevated superior vena caval mean pressure fell slowly, being 9 mm. Hg during tachycardia, 7 mm. during the [illegible]th to ninth and 6 mm. during the twelfth to eighteenth post-tachycardia beats of sinus rhythm. Four minutes after conversion it was 1 mm. Hg. The six brachial artery beats are also seen changing slowly.

as *flutter-fibrillation* (so called because atrial complexes are irregular in contour and occurrence and the atrial rate is faster than in flutter—occurring between 420 and 450—and slower than the usual fibrillation) atrial systolic waves are found. This suggests that when in the course of atrial fibrillation atrial rates fall into a slower range and are therefore less than the threshold required to initiate disordered atrial myofibriller contractions and atrial mechanical paralysis, it is possible for the atrial chambers to respond with discrete mechanical systoles. In this instance there is no longer tricuspid regurgitation.

Tricuspid and mitral regurgitation in atrial fibrillation may have still another significant effect. If pressure or indicator dilution curves secured during left and right heart catheterization were to be used as the only criteria to determine the presence of mitral or tricuspid valve insufficiency in a patient being considered for cardiac surgery, errors might result if this arrhythmia, which induces regurgitation in the absence of valve deformity, were present. The regurgitant blood may even cause confusion in the interpretation of angiocardiograms by producing a pseudo filling defect with each ventricular systole and thus erroneously suggest an atrial tumor.

The two physiologic features which distinguish flutter and fibrillation probably have direct bearing upon the incidence of atrial clots and embolic phenomena in the two arrhythmias. Atrial flutter seldom

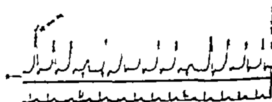


Fig. 14. Right atrial pressure curve in A-V dissociation with interference of [illegible] rhythm. For discussion see text.

if ever is associated with emboli whereas these may be relatively common complications with fibrillation. The constant and effective emptying of the atria as a consequence of discrete contractions would lessen sludging and clot formation in flutter, whereas atrial paralysis plus tricuspid and mitral regurgitation with overdistention of these atrial chambers in fibrillation would favor clotting.

Despite these differences in pressure characteristics, atrial flutter and atrial fibrillation share a common effect upon cardiac output. In both rhythms the resting level of output is decreased. In a group of 9 subjects with *atrial flutter*[4] the resting cardiac index was subnormal not only in 5 patients in congestive failure (cardiac indices ranged between 1.48 and 2.48 liters) and the 3 with heart disease and no failure (indices ranged between 1.67 and 2.10 liters), but also in the one individual aged 56 with paroxysmal atrial flutter and no heart disease (cardiac index of 2.57 liters).

Atrial fibrillation also produces a low resting cardiac output. In one man without heart disease who had paroxysmal atrial fibrillation and was studied by the authors, the resting cardiac index was definitely reduced (2.61 liters, a low figure for a 46 year old man) and on exercise the blood flow increased only to the low limit of normal. (He had an exercise factor of 185 when the normal figure is at least 800 and usually considerably greater, often reaching 1,000.[17]) This arrhythmia in patients with heart disease is widely accepted as depressing blood flow.

When both atrial flutter and fibrillation are converted to sinus rhythm, there is a rise in resting cardiac output. In 5 patients converted from flutter the increase in blood flow ranged from 25 to 50 per cent.[4]

Table II presents similar data on 2 patients in whom the basic rhythms changed between sinus and atrial fibrillation. In one case observations were made at rest and during supine leg exercise in sinus rhythm and at a later date when fibrillation had supervened. A drop of 43 per cent in resting cardiac index was present on the second study. On the other hand, the abnormal pressures in the pulmonary circulation, the limited exercise factor (the normal value is 800 c.c. or greater[17]) and the small increase in stroke volume are present in both studies, i.e., regardless of rhythm. In this man these latter physiologic variables are more likely regulated by the function of the ventricular myocardium per se and are less dependent on rhythm. If, however, organ flows are correlated with levels of cardiac output, there may be real compromises to coronary, cerebral, renal, adrenal, splanchnic and other visceral systems with the onset of atrial fibrillation.

The second patient in Table II was restored not only to a virtually normal level of cardiac output at rest (an index of 2.62 liters in a 71 year-old man) after conversion from atrial fibrillation to sinus rhythm

Table II. Hemodynamic data in 2 patients (during rest and exercise) in whom the basic rhythm changed between sinus and atrial fibrillation

Diagnosis	Rhythm	Pulmonary artery (Systolic/Diastolic Mean) Rest	Pulmonary artery (Systolic/Diastolic Mean) Exercise	Exercise factor	Cardiac index R	Cardiac index Exercise	Stroke volume Rest	Stroke volume Exercise
HASHD 65 M	NSR	33/1? 24	63/31 49	660	2.75	3.58	6	81
Rec. fr. CHF	A Fib	30/1? 17	57/29 39	393	1.57 (−43)	2.07	48	37
ASHD Severe CHF 71 M	A Fib	20/7 12	39/18 26	548	1.98	2.79	43	50
	NSR	25/7 16	39/11 4	1,014	2.62 (+32%)	4.70	58	175

For abbreviations see text.

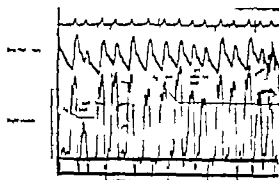


Fig 15 Brachial artery and right ventricular curves in atrial fibrillation The line drawn represent lowest and highest pulmonary artery diastolic pressure (P 1) For discussion see text

but also to a normal exercise factor which suggests in this instance that it was the arrhythmia per se which influenced exercise performance in this man and that his heart was much nearer to normal than that of the first patient in Table II

Another feature of the distortion of dynamics imposed by *atrial fibrillation* is seen in Fig 15 The variation in pulse pressure (or size) of the right ventricular beats is marked and there are some totally ineffective beats (ventricular systolic pressure less than pulmonary artery diastolic) in which the pulmonary valve does not open so that there is therefore no ventricular emptying and other beats that are only slightly effective Of the 15 beats depicted in Fig 15 four or five must produce minimal or no ejection into the pulmonary circulation Left ventricular ejection however occurs with every systole (see brachial artery curve) Hence the stroke volume by implication may be quite variable in this arrhythmia not only from beat to beat but also in one ventricle as compared to the other this may produce variations in pulmonary and hepatic blood volume and fluctuating pulmonary and abdominal symptoms

Summary and conclusions

In summary many clinically hidden but very real hemodynamic abnormalities exist in the case of cardiac arrhythmias to account for the bizarre symptoms which patients describe

Analysis of the intermittent arrhythmias reveals that tricuspid and probably mitral insufficiency are fairly frequent complications and may have far reaching effects on organ circulations other than the heart and lungs Furthermore ventricular asynchronism and pulsus alternans may be precipitated by them

In the common fixed arrhythmias atrial flutter and fibrillation and nodal tachycardia disturbances in cardiac output stroke volume and A V valve competence are emphasized as well as the behavior of these variables after resumption of normal sinus rhythm

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Retrograde conduction and isorhythmic dissociation in heart block

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In complete heart block in sinus rhythm Lead II of the electrocardiogram shows erect P waves dissociated from the QRS complexes On occasion under the same circumstances *Lead II shows both* erect and inverted P waves (Fig 1) The erect P waves are again dissociated from the QRS complexes but the inverted P waves follow rather closely some (not all) of the QRS complexes What is the explanation of these inverted P waves? Winternitz and Langendorf[1] reported this phenomenon and reviewed the literature They suggested that the inverted P waves were due to impulses of the idioventricular pacemaker conducted retrograde through the bundle of His Their hypothesis is persuasive in that it explains all the observed facts Their concept is strengthened by the demonstration of unidirectional conduction through muscle strips

Winternitz and Langendorf[1] postulated that impulses generated in the sinoauricular node (manifest as erect P waves in Lead II) enter the bundle of His and cause a refractory period in this tissue During the absolute refractory period retrograde transmission cannot occur During the relative refractory period retrograde transit is permitted with variable delay After the relative refractory period retrograde passage is facilitated and transmission time is constant It follows that both retrograde passage and the time required for this passage are dependent on the interval *after the capture of the bundle of His by the preceding sinus impulse* (See also legend to Fig 1) Others have accepted the possibility of retrograde conduction but have postulated a phase of supernormal conduction to explain the paradox of retrograde conduction in forward heart block

This paper reports (1) some factors influencing retrograde conduction that are acceptable with or without a postulate of a supernormal phase and (2) the results of an experiment that was planned to answer the question Does retrograde conduction depend upon a supernormal phase in the bundle of His? Since this experiment produced additional data on isorhythmic dissociation these data will be reported separately later in this paper

Case history

D S (J G H 63 1759) a 54 year-old white man was found to be hypertensive in 1960 *his blood pressure was 1/0 105 mm Hg He was treated* with rauwolfia Subsequently his blood pressure was 140/90 mm Hg

In 1961 two follow up electrocardiograms showed left bundle branch block On Feb 27 1963 he cam

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plained of mild dizziness the blood pressure was 120/80 mm Hg the pulse was 36 per minute and the ECG showed complete heart block (With complete heart block the QRS contour had changed the previous record had shown left bundle branch block) He was admitted for observation On March 5 his heart rate dropped unexpectedly to 16 per minute and an Adams Stokes attack resulted Intravenous isoproterenol hydrochloride (Isuprel) was effective in accelerating the heart rate When it proved impossible to wean him off the intravenous therapy an electrode catheter was placed in the right ventricle Before the catheter electrode was inserted we recorded and studied a number of long records as a matter of academic interest With the catheter in position we were able to alter the stimulus rate as reported below Later a permanent pacemaker was implanted Postoperatively the course was downhill and the patient died

Electrocardiograms

Retrograde conduction

Several long ECG records were studied Before the pacemaker was inserted all records showed an idioventricular focus controlling the ventricles There was never any evidence of forward conduction through the bundle of His Most of the records (not all) showed evidence of retrograde conduction Reciprocal beating was not seen All the records we have analyzed (Tables I and II) did not show either auricular or ventricular extrasystoles There was never any evidence of an independent nodal pacemaker (Shortly before the patient died a record taken out and mounted by the technician did show a few ventricular extrasystoles One of these ventricular extrasystoles is referred to later in the text) All records reproduced (Figs 1 to 3) are Lead II of the ECG

Factors influencing retrograde conduction Retrograde capture of the auricle is designated *P* When the retrograde impulse effects partial capture of the auricle it will share control of the auricle with the impulse generated in the sinoauricular node A fusion beat in the auricle will result This is designated *Pf*

In our material the mechanism described by Winternitz and Langendorf was apparent (see Fig 1) We confirm earlier observations that R P bears an inverse relationship to the preceding P R interval although this relationship is not strictly linear

Winternitz and Langendorf[7] predicted

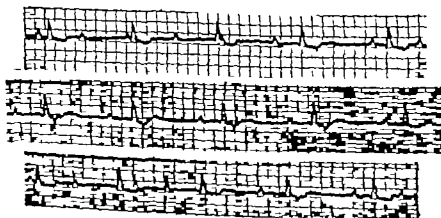


Fig *1* Three separate strips of the ECG are mounted A V dissociation and complete forward block are demonstrated *Inverted P waves follow some of the QRS complexes* The middle strip demonstrates a succession of retrograde P waves until the last beat when the P R interval has shortened and retrograde conduction is prevented Note also that retrograde conduction interferes with the sinus rhythm which is restored after the last QRS complex In the lower strip retrograde conduction is prevented after the first and last QRS complexes because of the proximity of the preceding P wave Retrograde conduction is prevented after the second QRS because a sinus P wave is buried in this QRS as is evident from the rhythm of the sinus node This interpretation is supported by the fact that this second QRS is taller than all the others recorded It is this buried P wave that renders the bundle of His refractory Attention is also drawn to the fusion P wave in the upper strip In the upper strip reference is made to the third QRS which is closely followed by a sinus P wave This sinus P wave with very short R P interval prevents retrograde conduction

Table I

Date	*Auricular rate (P–P interval)*	*Ventricular rate*	*P–R interval*	*R–P interval*	*Longest P–R interval not followed by retrograde conduction*
March 5, 1963, 3:40 A.M.	105 (57)	33	31	50	29
March 5, 1963, 3:40 P.M.	105 (57)	43	No retrograde conduction; R–P presumed to be longer than 57		
March 26, 1963	105 (57)	73	31	53	29
March 5, 1963, 1:45 P.M.	103 (58)	42	36	56	35
March 5, 1963, 10:15 A.M.	96 (62)	36	30	52	25
March 18, 1963	92 (65)	73	32	56	30
March 5, 1963, 9:30 A.M.	90 (67)	32	40	64	38
March 5, 1963, 11:00 A.M.	89 (67)	38	37	60	32
March 19, 1963, 7:35 P.M.	87 (69)	73	36	62	31
March 15, 1963	86 (70)	73	34	56	31
March 19, 1963, 3:30 P.M.	86 (70)	73	36	58	30
March 15, 1963	81 (74)	73	36	57	30
March 5, 1963, 3:30 A.M.	78 (77)	16	No retrograde conduction; R–P presumed to be longer than 77		
February 22, 1963	70 (86)	35	42	68	38
February 25, 1963	69 (87)	[illegible]	48	70	42
February 24, 1963	66 (91)	37	40	71	44
February 26, 1963	66 (91)	30	48	70	46
March 11, 1963	65 (92)	58	36	64	32
March 11, 1963	64 (94)	60	56	80	52
February 23, 1963	57 (105)	34	50	72	47

[illegible]

that retrograde conduction could not occur at auricular rates above 120 per minute. Our own results indicate that such a conclusion may not be valid. Table I is a summary of our factual observations. If we use the minimum P-R interval which permits retrograde conduction as an index of the refractory period of the bundle of His, a curious trend seems to be apparent. It seems that a more rapid rate of the sinoauricular node facilitates retrograde conduction. In any case, the faster sinus rates are associated with shorter P-R intervals and the slower sinus rates are associated with longer P-R intervals. If the trend referred to is meaningful, we have to postulate unknown factors obscuring the general pattern. (It is known that the refractory period shortens with faster stimulus rates and this may be the explanation of the general trend demonstrated in Table I.)

Planned study. When a catheter was used to pace the ventricles, retrograde conduction persisted unchanged. It was apparent that we had an opportunity for a planned study. According to the theory of Wintemitz and Langendorf[1] if the sinus node could be suppressed, continuous retrograde conduction should occur and R-P should be constant. According to the same theory, we could predict that suppression of the sinus node could be achieved if we could raise the rate of the stimulus pacemaker above that of the sinus node. For under these circumstances a single retrograde discharge of the sinus node would

lead to continuing retrograde conduction and suppression of the node.

In order to avoid undue acceleration of the ventricles, we planned the study with the patient under sedated sleep, during which we expected the sinus node to be subject to a natural slowing of rate. A long record was taken as a base line. Small changes in the rate of the electrical pacemaker were then induced and serial records were taken.

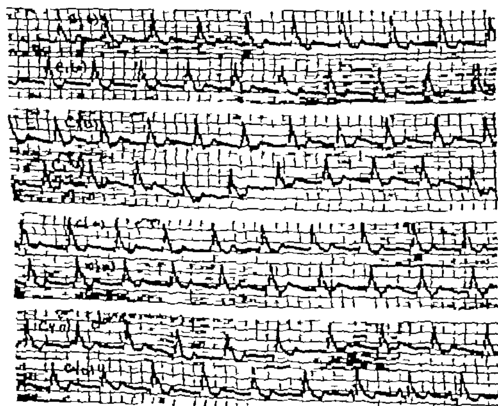
Results of planned study. The results will be analyzed further later in this paper. Here a brief note will be recorded. Fig. 3 (Section D₁) shows that continuing retrograde capture of the auricle (P) and suppression of the sinus node were achieved at a stimulus rate of 85. Figs. 2 and 3 and Table II also show that continuing retrograde conduction with long series of fusion P waves (PT) was achieved at stimulus rates of 65, 67, 68, and 71.

Electrocardiograms

Isorhythmic dissociation

Under certain circumstances, if two separate strips of heart muscle are placed in contact with one another, then both strips of muscle will beat synchronously. Segers[3] has shown that each strip of muscle continues under the control of its own pacemaker. Thus each pacemaker maintains autonomous control, but the two pacemakers synchronize. This phenomenon is conveniently and appropriately labeled *isorhythmic dissociation*. This concept is proving to be useful in clinical electrocardiography in the interpretation of certain arrhythmias. (Under these circumstances an occasional slight asynchronism in isorhythmic dissociation will indicate that neither pacemaker has been suppressed by the other.)

Results of planned study. The results are shown in Figs. 2 to 4 and are summarized



F[illegible] Section C [illegible] Stimulus rate 65/min. Isorhythmic dissociation. *Section C* [illegible] Stimulus rate 68/min. [illegible] through [illegible] *Section C* [illegible] Stimulus rate [illegible]/min. Sinus node [illegible]. *Section C* Stimulus rate 6[illegible]/min. Sinus node [illegible] further.

in Table II. The entire material is reproduced and it is reproduced in the proper chronological sequence. This is essential because the change (slower or faster) in the rate of the stimulus pacemaker is regarded as cause and the resultant change in rate of the sinus node is regarded as effect. The labels C_1 to C_5 and D_1 to D_6 have been used to designate the sections recorded. Each of the sections in Figs. 2 and 3 is a reproduction of 18 seconds of continuous recording.

Discussion

Mechanism of retrograde conduction in heart block. The paper of Winternitz and Langendorf[1] discusses the mechanism proposed to explain the paradox of retrograde conduction in heart block. According to these authors the impulse of the sinus P wave enters the bundle of His and renders it refractory. During the absolute refractory period retrograde conduction is not possible. During the relative refractory period retrograde conduction is delayed with variable prolongation of P-R. An alternative theory is that the impulse of the sinus P wave entering the bundle of His creates in this bundle a supernormal phase which permits retrograde conduction. In one case the sinus P wave hinders retrograde conduction which will not occur unless the hindering influence is sufficiently remote in time. In the other case the sinus P wave promotes for a fleeting moment that retrograde conduction which would otherwise be impossible.

We are able to resolve this conflict of hypotheses in three different ways.

1. Suppose a ventricular extrasystole were strategically placed soon after retrograde capture has occurred. Under these circumstances the sinus P wave is suppressed for a few moments only. According to the theory of Winternitz and Langendorf a second retrograde conduction would be expected. We have seen a single instance of this sort in the case now being reported. Scherf and Schott[4] have published a similar record (see their Figure 92), although they have not commented on its significance.

2. A more prolonged suppression of the sinus node would render a more decisive judgment in this context. This is exactly what was done in our planned study (Section D_3). Continuous retrograde conduction with a constant R-P was predicted and achieved. (Both the absolute and relative refractory periods previously postulated have now been abolished.)

3. Our planned study has yielded an unexpected bonus in the entirely astonishing series of fusion P waves seen in our material. Here the argument is equally

Table II

Section recorded	*Rate of stimulus per minute*	*Total length of record in seconds*	*Events observed*
C_1	65	104	Synchronous dissociation. (Occasional P wave activity seen before stimulus or on downstroke of QRS)
C	68	45	Fusion P waves throughout
C	66	51	At first sinus node slows below rate of stimulus. Later it speeds up to escape control
C	62	84	*At first sinus node slows below rate of stimulus. Later it speeds up to escape control*
C_5	58	56	Sinus pacemaker is always faster than stimulus
D	64	40	No retrograde conduction. Sinus node under control of pacemaker (See Fig. 4)
D_2	71	36	Retrograde capture of auricles is followed by a succession of fusion P waves
D	83	21	Continuous retrograde capture of the auricle
D_4	67	26	Fusion P waves throughout
D_5	63	25	At first sinus node slows below rate of stimulus. Later many fusion P waves are seen
D_6	60	28	Sinus pacemaker is always faster than stimulus

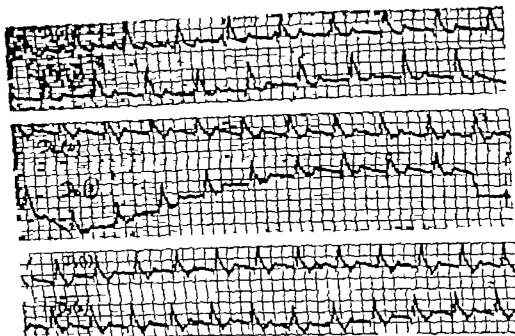


Fig *Section D* Stimulus r te 64/min No retrograde conduction *Section D* Stimulus rate l/min P followed by Pf as sinus node accelerates *Section D* Stimulus rate 85/min I throughout and R P con ta t Sinus node is suppressed Note contrast between I and Pf

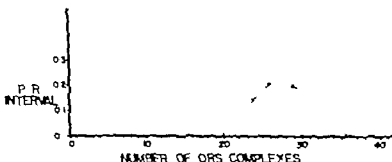


Fig 4 Graph showing the relationship of the sinus induced P w es to the stimulus induced QRS complexes recorded in Section D P I interval zero means that the P wave i buried in the QRS complex The P R interval is never long enough to permit retrogra le conduction The graph shows a ariation of the phen omenon of *accrochage reported* by Segers (The term *accrochage* im plies temporary linkage of the rates of the two card ac pacemakers) Section D of Fig 3 represents the f rst 18 seconds of this graph

compelling The sinus P wave has not been suppressed but it s entry to the bundle of His is prevented by interference in the auricles Once again continuous *retro* grade conduction is permitted

Effect of rate of stimulus pacemaker on rate of sinus node The work here *reported* offers evidence in the human heart *of the* range of phenomena observed by Segers[1] in the frog heart When the rates of the two pacemakers are close enough isorhyth mic dissociation is apparent (records C_1 and C) Record D appears to be a variant of the phenomenon of *accrochage* (Fig 4) Note also the fusion beats discussed later But even at closely related rates the influence or control may be temporarily lost (records C_3 and C_4) During isorhyth mic dissociation the independent action of two pacemakers is made apparent by oc

casional lack of synchronization (record C_1) When the rates of the two pacemakers are sufficiently far apart each is likely to go its own way (records C_6 and D_6)

It is already suggested that the rate of the sinus node was influenced by the rate of the stimulus In addition on three separate occasions a slowing of the stimulus—from 68 to 66 from 66 to 62 and from 67 to 65—was followed by a temporary slowing of the sinus node below the new stimulus rate a curious overshoot effect Yet when the rate was speeded up from 64 to 71 temporary retrograde conduction was followed by a series of fusion beats

At rates of 65 67 68 and 71 an entirely astonishing series of fusion P waves are seen The fusion P wave is an exquisitely sensitive index of the linking of both pacemakers in relation to one another In the zone under consideration a constant difference in rate of the two pacemakers of one beat per minute would not permit more than three fusion beats in succession and then a changing contour of fusion would be apparent We are led to the conclusion that the sinus node is subject to rigid control at these varying rates Both pacemakers beat at the same rate and both maintain a meticulously unchanging out of step relationship

Finally in records C_3 and D_8 32 P P intervals could be measured accurately The auricular rate in these records apparently freed from the control of the slower stimulus pacemaker ranged from 60 to 67 per minute Yet both before record C_3 and after it long series of fusion P waves occurred at stimulus rates of 68 and 71 per minute respectively (records C and D) If a spontaneous sinus arrhythmia were responsible for some of the over shoots and supposed links of atrial and ventricular rhythm referred to above then clearly this sinus arrhythmia must have been suppressed during the many long series of fusion beats recorded

Summary

In a case of heart block with retrograde conduction a catheter electrode was introduced to pace the ventricles Under these circumstances a planned study was undertaken The results indicate (1) Alterations in rate of the stimulus pacemaker in a narrow range around the natural rate of the sino auricular node influence the rate of the latter to follow the induced changes in the artificial stimulus (2) Continuing retrograde conduction to the auricle can occur when the sinus node is suppressed by raising the rate of the stimulus pacemaker (3) Continuing retrograde conduction to the auricle can occur with long series of fusion P waves in the auricle It is concluded that retrograde conduction to the auricle is not dependent on a supernormal phase phenomenon

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Electrocardiographic manifestations of ventricular hypertrophy, a computer study of ECG-anatomic correlations in 319 cases

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Although many criteria have been proposed for the electrocardiographic diagnosis of left ventricular hypertrophy (LVH) all fall short of the ideal of a high degree of sensitivity plus a high degree of specificity (a low incidence of false positives).

These criteria have arisen from widely variable case material. Some are based on case material selected by clinical techniques and some on cases in which LVH was proved at autopsy. Most criteria have been selected empirically, although good retrospective reasons for the occurrence of these factors in LVH can be offered. The application of such criteria to large groups of cases studied at autopsy has been presented in several excellent reviews over the past few years,[1-4] with comparisons of their relative sensitivity and specificity.

In view of the accepted limitations of established criteria and the continued need for more accurate criteria, we have elected to start anew by re-examining the empirical relationship between heart weight, left and right ventricular thickness, and various electrocardiographic measurements, with the hope that these studies might provide new insight into these relationships and a more objective basis for new criteria for the diagnosis of left ventricular hypertrophy. This approach has been greatly aided by the recording of the data on punch cards and subsequent statistical analysis by means of an IBM 7072 computer.

Material and methods

No attempt was made to select a particular group of cases. Serial autopsies were surveyed, and all cases were included in which the following criteria were met: (1) satisfactory electrocardiograms had been recorded within a year prior to death, (2) adequate autopsy observations of heart weight and size had been made, (3) no significant pericardial fluid or cardiac displacement (by tumor masses, etc.) was present, and (4) no bundle branch block or other significant conduction disturbances producing QRS prolongation beyond 0.12 second were present. The latter exclusion was thought to be necessary in the present

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study in view of the confusion independent of heart weight introduced by these conduction abnormalities. All subjects were adult males, since the autopsy material was from a Veterans Administration hospital.

Three hundred and nineteen (319) cases were selected by the above-mentioned method. From this group the electrocardiograms were coded and analyzed without references to the anatomic findings. The following observations were recorded: largest R or S in limb leads, largest S (or Q) in right precordial leads, largest R in left precordial leads, the left ventricular activation time (the time from onset of QRS to the peak of R) in V_5 or V_6, the electrical axis of QRS in the frontal plane, the location of the QRS transition in the precordial leads, the QRS duration, and the presence and type of S-T segment deviation.

After completion of the ECG analysis, certain clinical data (i.e., weight, height, history of digitalization and congestive failure) and pertinent autopsy data (heart weight, LV thickness, RV thickness, the prosector's impression of ventricular enlargement, etc.) were recorded from the autopsy protocol.

All data were transferred to punch cards for subsequent analysis with the aid of an IBM 7072 computer.

Results

As a first approach to the study of significant relationships between heart weight and other measurements, cross correlations were done with the linear variables, as shown in the following section. Relationships between heart weight and nonlinear variables were evaluated by other techniques as shown in a later section. In order to evaluate the deviation of the heart weight from the normal heart weight for a subject, the difference between the observed heart weight and the ideal heart weight calculated from the formula proposed by Zeek was correlated in the same manner and is included in the subsequent discussion.

A. Linear variables

TOTAL HEART WEIGHT. Heart weight was found to be significantly correlated with other cardiac measurements such as left ventricular thickness and right ventricular thickness (Table I). Heart weight was also significantly correlated with the patient's body weight (Table II). With respect to electrocardiographic measurements (Table III), heart weight was significantly correlated with the R wave amplitude in the limb leads, the S wave amplitude in the precordial leads, the R wave amplitude in the precordial leads, the ventricular activation time, the QRS duration, and the transition zone in the precordial leads. Thus it is seen that total heart weight is correlated with all the electrocardiographic parameters listed. With respect to the degree of correlation, the best correlation was seen with S wave amplitude in the precordial leads and with ventricular activation time.

Deviation from normal heart weight correlates with the same variables and to approximately the same degree as the total heart weight.

It was reasoned that certain electrocardiographic parameters might be altered from normal only by the presence of severe grades of hypertrophy, and therefore correlation would exist between heart weight and these parameters only in the hypertrophied hearts. On the other hand, other parameters might correlate with heart weight throughout the span of heart weights. In order to study this possibility, the total group was subdivided into two smaller groups according to heart size (Table IV). There were 194 hearts which could be classified as hypertrophied according to the Zeek criteria (Zeek positive). In this group it was found that there was no longer a significant correlation between heart weight and R wave amplitude in the limb leads. The correlation with QRS amplitude in the precordial lead was below the 1 per cent level of significance. On the other hand, highly significant correlations between heart weight and ventricular activation time, QRS duration, and transition zone were present. When deviation from normal heart weight rather than heart weight per se was considered, the correlations with ventricular activation time, QRS duration, and transition zone were improved, and a highly significant correlation with S wave depth in the precordial leads was again seen.

There were 125 hearts which fell within the normal weight range according to

Table I Total group Correlation of heart weight with other heart measurements

	L V thickness	*R V thickness*
Heart weight (N = 286)	< 001	< 001
Deviation from normal heart weight (N = 273)	< 001	< 001

N = Number of observations In th[illegible] d subseq[illegible] t tables th[illegible] significance le[illegible] el p[illegible] presented rather th[illegible] th[illegible] correlat[illegible] coefficient [illegible] The [illegible] values [illegible] obtained by [illegible] tables

Table II Total group Correlation of heart weight with age and body size

	Age	*Body height*	*Body weight*
Heart weight (N = 317)	N S	N S	< 01
Deviation from normal heart weight (N = 307)	N S		< 01

Corr [illegible] calculated [illegible] body h[illegible] ght [illegible] [illegible] d[illegible] v[illegible] from [illegible] normal h[illegible] art weight

Table III Total group Correlation of heart weight with ECG measurements

	R wave amplitude in L L	*S wave amplitude R P L*	*R wave amplitude in L P L*	*Ventricular activation time*	*QRS duration*	*Transition zone*
Heart weight (N = 319)	< 01	< 001	< 001	< 001	< 001	< 001
Deviation from normal heart weight (N = 304)	< 01	< 001	< 001	< 001	< 001	< 001

L L Limb leads *R P L* Right precordial lead *L P L* Left precordial leads

Zeek criteria In this group none of the electrocardiographic variables showed any significant correlation with heart weight Thus it might be concluded that the correlation between heart weight and the electrocardiographic parameters is one which appears only with hypertrophy and is not a linear correlation over the entire range of heart weights

There are other incidental correlations which were unexpected and therefore worthy of emphasis (Table V) In the total group age was negatively correlated with QRS amplitude As might be expected this correlation was not seen in the hypertrophied group since large hearts occur at all ages but in the nonhypertrophied group a significant negative correlation with QRS amplitude is seen in spite of a positive correlation between age and heart weight Thus some factor associated with increasing age is seen to decrease the apparent QRS amplitude in spite of an increasing heart weight

LEFT AND RIGHT VENTRICULAR THICKNESS It was expected that left ventricular thickness and total heart weight would correlate with the same ECG parameters and to approximately the same degree However there were some striking deviations from this expected pattern plus certain other unexpected differences in cross correlations between left and right ventricular thickness and certain ECG parameters (Table VI)

In the total group left ventricular thickness correlates significantly with all QRS amplitude parameters with ventricul

activation time and with the position of the transition zone. *Right* ventricular thickness is found to be more highly correlated with ventricular activation time than is left ventricular thickness (correlation coefficient is higher although both are at 1 per cent significance level). In the hypertrophied group right ventricular thickness shows a borderline (5 per cent) level of positive correlation with ventricular activation time. In the nonhypertrophied group there was a borderline negative correlation between left ventricular thickness and ventricular activation time.

It was postulated that congestive failure might produce an increased right ventricular thickness, as has been reported by Jones[5] and at the same time prolong the ventricular activation time, thus establishing the observed correlation. For this reason, the group of hearts which met the Zeek criteria for hypertrophy were further separated into two groups: (1) a group in which failure had not been present during the patient's lifetime, and (2) a group in which failure had been clearly noted during the patient's lifetime. Those in which this determination could not be made were not included. These two groups were approximately the same size, 48 and 47 subjects, respectively. It was found (Table VII) that in the group without congestive failure there was no significant correlation between heart weight and ventricular activation time. On the other hand, in the group which had experienced congestive failure during life there was an extremely high correlation. In this group there was also a very high correlation between ventricular activation time and right ventricular thickness. Thus, the hypothesis that the presence of congestive failure increases right ventricular thickness and at the same time increases the duration of the ventricular activation time seems to be confirmed. Whether this is a cause and effect relationship (i.e., increased right ventricular thickness causes increased ventricular activation time) is not established by these data.

B. Nonlinear variables. The presence of left axis deviation and the presence of S-T segment shift were considered to be nonlinear variables (evaluated as present—not present or positive-negative). The relationship between these variables and heart weight was evaluated by means of the Kolmorogov-Smirnov two-sample test,[6] and the results are presented as converted chi-square values with significance levels in Tables VIII-X.

S-T SEGMENT DEVIATION. There is considerable variation in the interpretation of a significant S-T segment shift from one person to another. In order to evaluate various degrees of sensitivity in interpretation, a positive S-T segment shift was defined in two ways, and each was evaluated separately. First, the presence of any S-T segment depression exceeding 0.5 mm. in the limb leads or in the left precordial leads was considered to be positive, regardless of configuration, slope, or position of the J point. This is identified in the tables and discussion as "typical + atypical" S-T segment shift. Next, the presence of typical "left ventricular strain" type S-T segment depression, with an S-T segment sloping away from a less deviated J point into an inverted T wave and exceeding 0.5 mm. in the limb leads or in the left precordial leads, was considered to be positive. This is identified in the tables and discussion as "typical" S-T segment shift.

As can be seen in Tables VIII and IX, a significant relationship was seen when both definitions of a positive S-T segment shift were used. The presence of "typical + atypical" S-T segment shift showed a higher chi-square value, but both were highly significant.

The role of digitalis administration must be considered in the above-mentioned relationship. The administration of digitalis would be expected to be more frequent in patients with large hearts and might therefore account for the significant relationship. For this reason, those patients in whom there was no history of digitalis administration prior to death were considered separately from those with such a history (Tables X and XI). There were 230 patients with no history of digitalis administration. In this group there was a highly significant relationship between heart weight and the presence of "typical + atypical" S-T segment shift. There was also a highly significant relationship be-

Table IV *Subgroups Correlation of heart weight with ECG measurements in hypertrophied (Zeek positive) and nonhypertrophied (Zeek negative) hearts*

	R wave amplitude in LL	*S wave amplitude in RPL*	*R wave amplitude in LPL*	*Ventricular activation time*	*QRS duration*	*Transition zone*
Zeek positive						
Heart weight (N = 194)	NS	< 05	NS	< 001	< 01	< 01
Deviation from normal heart weight (N = 184)	NS	< 01	NS	< 001	< 01	< 01
Zeek negative						
Heart weight (N = 123)	NS	NS	NS	NS	NS	NS
Deviation from normal heart weight (N = 120)	NS	NS	NS	NS	NS	NS

Table V *Total group and subgroups Correlation of age with QRS-amplitude parameters and heart weight*

	R wave amplitude in LL	*S wave amplitude in RPL*	*R wave amplitude in LPL*	*Heart weight*
Age total group (N = 317)	< 01 (−)	< 01 (−)	< 05 (−)	NS
Age Zeek positive (N = 193)	NS	NS	NS	NS
Age Zeek negative (N = 124)	< 01 (−)	< 01 (−)	NS	< 01

Table VI *Total group and subgroups Correlation of left and right ventricular thickness with ECG parameters in total group hypertrophied (Zeek positive) and nonhypertrophied (Zeek negative) subgroups*

	R wave amplitude in LL	*S-wave amplitude in RPL*	*R wave amplitude in LPL*	*Ventricular activation time*	*QRS duration*	*Transition zone*
Total Group						
LV thickness (N = 286)	< 01	< 001	< 001	< 01	NS	< 001
RV thickness (N = 277)	NS	NS	NS	< 01	NS	< 001
Zeek positive						
LV thickness (N = 173)	< 05	< 01	< 01	NS	NS	< 001
RV thickness (N = 167)	NS	NS	NS	< 05	NS	NS
Zeek negative						
LV thickness (N = 113)	NS	NS	NS	< 05 (−)	N	NS
RV thickness (N = 110)	NS	NS	NS	[illegible]		

tween heart weight and the presence of typical S-T segment shift. Again the chi square value was higher with typical + atypical S-T segment shift.

There were 89 patients in whom there was a history of digitalis administration. In 18 of this group there was no S-T segment deviation. In 49 the S-T segment deviation was considered to be typical and in another 31 the S-T segment devi-

Table VII. Correlation of heart weight, L.V. thickness, and R.V. thickness with ventricular activation time in subjects with and without congestive heart failure

	Ventricular activation time
Hypertrophy, no failure (N = 48)	
Heart weight	N.S.
L.V. thickness	N.S.
R.V. thickness	N.S.
Hypertrophy with failure (N = 47)	
Heart weight	< .001
L.V. thickness	N.S.
R.V. thickness	< .001

Table VIII. Total group. Relationship between deviation from normal heart weight and presence of typical + atypical S-T segment shift

	Deviation from normal heart weight (grams)							Total
	−50	0	+50	+100	+200	+300	+600	
S-T segment shift—Absent	43	36	36	27	20	6	6	174
S-T segment shift—Present	15	6	10	13	38	27	36	145
Total	58	42	46	40	58	33	42	319

Converted chi square = 83.1
Significance level = < .001

Table IX. Total group. Relationship between deviation from normal heart weight and the presence of typical S-T segment shift

	Deviation from normal heart weight (grams)							Total
	−50	0	+50	+100	+200	+300	+600	
S-T segment shift—Absent	50	41	43	33	41	14	16	174
S-T segment shift—Present	8	1	3	7	17	19	26	81
Total	59	42	46	40	58	33	42	319

Converted chi square = 52.7
Significance level = < .001

ation was atypical The presence of typical + atypical S T segment deviation did not show a significant relationship with heart weight The presence of typical S T segment deviation showed a relationship of borderline significance (p = 05) as is shown in Table XII

Thus when there is a history of digitalis administration S T segment deviation becomes unreliable as a differentiating

Table X Patients with no history of digitalis administration Relationship between deviation from normal heart weight and typical + atypical S T segment shift

	Deviation from normal heart weight (grams)			Total
	To +50	+51 to +200	Above +200	
S-T shift—Absent	107	43	6	156
S T shift—Present	21	30	23	74
Total	128	73	29	230

Converted chi square = 39 0
Significance level = < 001

Table XI Patients with no history of digitalis administration Relationship between deviation from normal heart weight and typical S T segment shift

	Deviation from normal heart weight (grams)			Total
	To +50	+51 to +200	Above +200	
S T shift—Absent	119	63	16	198
S T shift—Present	9	10	13	32
Total	128	73	29	230

Converted chi square = 16 1
Significance level = < 001

Table XII Patients with a history of digitalis administration Relationship between deviation from normal heart weight and typical S T segment shift

	Deviation from normal heart weight (grams)			Total
	To +50	+51 to +200	Above +200	
S-T shift—Present	3	14	32	49
S-T shift—Absent	15	11	14	40
Total	18	25	46	89

Converted chi square = 8 7
Significance level = < 05

Table XIII. Total group. Relationship between deviation from normal heart weight and left axis deviation

	Deviation from normal heart weight (grams)			Total
	To +50	+51 to +200	Above +200	
LAD (0°)				
Present	29	36	33	98
Absent	117	62	42	221
	(Converted chi square = 15.3; p = < .001)			
LAD (−15°)				
Present	18	29	28	75
Absent	128	69	47	244
	(Converted chi square = 21.9; p = < .001)			
LAD (−30°)				
Present	16	19	25	60
Absent	130	79	50	259
	(Converted chi square = 16.1; p = < .001)			

criterion for the presence of hypertrophy unless typical. Even in this case it is a relatively poor differentiating criterion.

It should be mentioned that although a careful search of the records of each patient was carried out, there is still a possibility that digitalis had been administered prior to hospitalization in some patients in whom no such history was obtained. Since this would be expected to occur more often in those with large hearts, it is possible that this factor might still play a part in the significant relationship between heart size and the presence of S-T segment deviation. It seems unlikely that this has played a very large role.

LEFT AXIS DEVIATION. As in the case of S-T segment deviation, left axis deviation can be defined in various ways. For this reason, three definitions were established and each was evaluated separately. These are as follows: (a) Frontal plane QRS axis is equal to or more negative than 0°. This is termed *LAD (0°)* in subsequent tables and discussion. (b) Frontal plane QRS axis is equal to or more negative than −15°. This is termed *LAD (−15°)*. (c) Frontal plane QRS axis is equal to or more negative than −30°. This is termed *LAD (−30°)*. As seen in Table XIII, all three definitions of left axis deviation showed a highly significant relationship with heart weight. LAD (−15°) showed a higher converted chi square value.

Discussion

In this study, we have deliberately made no attempt to select patients with respect to the type of heart disease or to an expected type of hypertrophy (i.e., left or right). Instead, we have selected cases on a serial basis, provided that certain criteria were met. Thus, the present study can be considered to be an exploration of the empirical relationships between electrocardiographic parameters and heart weight irrespective of right or left hypertrophy. Left and right ventricular thickness are also considered, and their relationships to the same electrocardiographic parameters are considered. Because of the higher incidence of left ventricular disease in such a series of adult male patients, the data have been more heavily weighted by patients with this type of hypertrophy. This has been useful in one respect, since it has emphasized the frequent occurrence of increased right ventricular thickness in left ventricular disease, particularly when failure has been present during life. On the other hand, it has made it difficult to consider the effect of increased right ventricular thickness independent of increased left ventricular thickness. To further evaluate this problem, a separate selected group of autopsied cases showing increased right ventricular thickness must be selected and studied separately.

The fact that an increasing heart weight

was highly correlated (p = less than .001) with an increasing thickness of both the right and left ventricular walls emphasizes the fact that some of our conventional criteria, generally derived from groups of patients who are considered to have "pure" LVH on clinical grounds, may not reflect left ventricular thickness alone. These may be related to conduction disturbances which are in turn related to the underlying heart disease. The unexpected high correlation of ventricular activation time with right ventricular thickness is a case in point and may throw some light on the varied emphasis placed on this ECG parameter by different observers. In a series in which LVH is defined by left ventricular thickness or left ventricular weight, the reliability of this parameter would be judged to be minimal. On the other hand, in a series in which LVH is defined on the basis of total cardiac weight or on the basis of purely clinical criteria, it might be judged to be highly reliable. In this case, it is speculated that the relationship is created by the simultaneous presence of conduction disturbances and increased right ventricular thickness in more severe heart disease (as evidenced by congestive failure).

The lack of a significant association between QRS amplitude and other ECG parameters over the entire range of heart weights also emphasizes this point. If the relationship between heart size and QRS amplitude were a direct one, one might expect the relationship to exist over the entire range of heart weights. The observed relationship was one in which a correlation existed only in those hearts above accepted limits of normal weight, suggesting that muscle mass is not the parameter to which amplitude is primarily related, and that some other factor associated with heart disease may be more important.

This study has demonstrated a significant correlation between heart weight and QRS amplitude measurements, such as R wave amplitude in the limb leads, S wave amplitude in the right precordial leads, and R wave amplitude in the left precordial leads. Precordial lead amplitude demonstrated a distinctly higher degree of correlation with heart weight than did limb lead amplitude. Although both precordial S wave amplitude and R wave amplitude were highly correlated with heart weight, S wave amplitude demonstrated a slightly higher degree of correlation.

The negative correlation of age with limb lead and right precordial lead QRS amplitude is of considerable interest, especially in view of the fact that age is not correlated with heart weight in the total group and is positively correlated with heart weight in the nonhypertrophied group. This may reflect the effect of progressive emphysema with increasing age. Hiss[7] has reported a similar observation (gradual diminution of QRS amplitude with increasing age and independent of the effects of QRS axis rotation and body weight). This finding raises the additional question whether single amplitude criteria for a diagnosis of hypertrophy should be applied to all adult age groups.

A significant correlation was also seen between heart weight and QRS duration, the position of the QRS transition zone in the precordial leads, the presence of S-T segment shift, and the presence of left axis deviation. The electrocardiographic effects of the administration of digitalis considerably limit the usefulness of S-T segment shift as a parameter for the diagnosis of ventricular hypertrophy, but it is interesting to note that the presence of "typical" S-T segment shift still has some usefulness in this situation.

Although these observations, in their present form, are not of particular value in the electrocardiographic quantitation of the degree of hypertrophy in a given heart, they provide a basis for evaluating current criteria and for constructing new ones with an aim toward improved specificity. New criteria based on these observations have been devised and are being tested on an independent group of hearts and electrocardiograms.

Summary

Significant correlations were found between heart weight and QRS amplitude measurements. The most significant were S wave depth in the right precordial leads and R wave height in the left precordial leads. These correlations were not seen

throughout the range of heart weights but only when the heart weight was above normal Heart weight was also correlated with QRS duration the position of the QRS transition zone in the precordial leads the presence of S T segment shifts and the presence of left axis deviation The administration of digitalis considerably limits the usefulness of S T segment shift as a parameter which differentiates normal from large heart weights Left ventricular activation time was found to be correlated with heart weight but was more closely related to right heart thickness than left heart thickness

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Comparative study of electrocardiograms of healthy premature and full-term infants of similar weight

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In a follow up study of premature infants during their first year of life surprisingly few differences were found between infants who weighed 1 500 grams or less at birth and those who weighed 1 500 grams or more[1] Even differences between premature and full term infants of the same age seemed to be confined primarily to the immediate neonatal period However comparison was based on reported values for full term infants which may be open to some criticism There appeared to be good evidence that electrocardiographic maturation took place since intervals increased in duration and amplitudes of the Q R S and T waves became much larger with age This was in accord with the findings of Ziegler but how many of those infants were serially examined is not clear This study was undertaken to obtain further proof of such maturation by comparing tracings of 37 healthy premature and 68 healthy full term infants of similar weight

Method

Premature infants ranged in age from 21 days to 5 months with a mean of 69 days Only 2 infants weighed more than 2 000 grams at birth since the course and the mortality rate of infants in this weight group closely resemble those of mature infants To minimize changes associated with extrauterine adaptation all term infants were 5 or 6 days old (mean 136 hours) A further subdivision based on weight was made because of the disparity in age of the premature infants those who weighed 3 350 grams or less (A) were compared to those who weighed 3 355 grams or more (B) There were 17 premature and 38 full term infants in Group A and 20 premature and 30 full term infants in Group B

Recordings on premature infants were taken at a paper speed of 75 mm per second on a 2-channel photographic recorder whereas those on full term infants were taken at 100 mm per second with a 4-channel jet writer on which linearity was periodically checked All electrocardiograms were taken by the author at full standardization (1 mV = 1 cm) and great care was exercised in the selection of electrode positions and in the application and removal of paste Readings were made with a magnifying lens according to the recommendations of the Criteria Committee of the New York Heart Association No sedation was given to any of the infants

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Table I Comparison of means in premature and full term infants of similar weight

	Premature		*Full term*	
Number	17	20	38	30
Group	A	B	A	B
Weight (Gm)	2 740	3 870	2 978	3 751
Age	44 days	90 days (19)	137 hr	134 hr
Axis	76 3 (16 09)	69 9 (19 31)	134 4 (27 64)	126 9 (24 57)
Heart rate (beats/min)	159 (22 33)	159 (22 47)	161 (17 80)	158 (22 80)
P amp u	1 205 (514)	1 10 (300)	1 485 (628)	1 45 (393)
I wa ei dur	048 (0048)	051 (0076)	049 (0173)	053 (0078)
P R ; int	104 (0128)	097 (0083)	098 (014)	101 (015)
QRS dur *	045 (0071)	048 (0040)	051 (0074)	053 (0081)
Q T int	241 (0187) (16)	245 (0495)	264 (0236)	272 (0285)
Q P ; time	0144 (0060)	0165 (0052)	019 (0046)	022 (0063)

M QRS Q T d Q-R interval longer premature than in full term infants Group A 3,250 Gm or less Group B 3,333 Gm or more Number ... corresponds to the number of ... used ... number ... Figures in parentheses below means = standard deviation.
Measured 1 10 mV
Measured second
= p < 01 = p < 005

Other details in this regard have been published elsewhere[1]

Results

Age weight and heart rate The mean age of premature infants in Group A was 44 days with 2 infants more than 2 months old and in Group B 90 days with 3 infants less than 2 months old whereas that of full term infants was 137 and 134 hours respectively The mean values for weight were similar for both main groups 2 740 and 3 820 grams for premature infants and 2 978 and 3 751 grams for full term infants None of the premature infants weighed less than 2 500 nor more than 4 560 grams and 4 of them were included in both weight groups Full term infants had a minimum weight of 2 360 grams (birth weight not having been regained at discharge) a maximum of 4 640 grams and none was included in both weight groups Neither weight nor age was found to influence heart rate Both minimum and maximum values were similar as were the means (159 for premature and 160 for full term infants) (Table I Fig 1)

Intervals

P WAVE DURATION Premature infants in Group A had a mean P wave duration of 0 048 sec With the exception of the heaviest and oldest infant this interval varied from 0 04 to 0 05 sec The mean for Group B was 0 051 sec and 7 infants had values of 0 055 to 0 065 sec Full term infants (weight groups combined) tended to have a greater number of values of 0 055 sec or more 25 infants (42 6 per cent) as compared to 8 (21 per cent) premature infants

P R INTERVAL Only 4 premature infants regardless of weight group had an interval of less than 0 09 or more than 0 11 sec Of these 2 had relatively rapid heart rates (174 beats per minute each) and 1 was the youngest in the series (3 weeks old) The range was slightly greater in full term infants although the means were the same (0 100 sec) Intervals of 0 085 sec or less

and 0 115 sec or more occurred in 19 5 and 14 per cent respectively of full term infants and in 5 4 per cent each of premature infants

Full term infants of lighter weight appeared to have shorter intervals i e 0 09 sec or less Seventeen (44 7 per cent) full term infants in Group A were in this range as compared to 2 (11 8 per cent) premature infants in Group A ($p < 05$)

QRS DURATION The normal range of this interval in infancy appears to be very narrow if subjects with conduction disturbances such as bundle branch block or Wolff Parkinson White syndrome are excluded In premature infants the interval ranged from 0 04 to 0 055 sec with a mean of 0 047 sec and in full term infants from 0 04 to 0 06 sec with a mean of 0 052 sec Full term infants had a higher percentage of longer intervals and premature infants of shorter intervals That is 19 premature infants (51 3 per cent) had an interval of 0 045 sec or less as compared to 12 full term infants (17 6 per cent) whereas no premature infant had a value of 0 06 sec and 14 full term infants did have (20 6 per cent) ($p < 0005$)

Q R TIME

Lead V_1 (onset of intrinsicoid deflection) Although the range was similar for both premature (0 005 0 035 sec mean 0 015 sec) and full term infants (0 01 – 0 035 sec mean 0 020 sec) premature babies again tended to have shorter and full term babies longer intervals A Q R time of 0 015 sec ≥ and 0 02 sec ≤ was present in 83 3 and 16 7 per cent of premature infants and in 27 9 and 72 1 per cent of full term infants ($p < 0005$) Of the 4 premature infants with a Q R time of 0 025 sec or more one had the slowest heart rate in the group and another was the only infant without an S wave in this lead None had any specific measured electrocardiographic or other deviation in common

Q T INTERVAL

Lead II As in the case of the QRS and Q R time premature infants had shorter and full term infants had longer Q T intervals Although the range and means were similar for premature infants in both groups (A 0 195 0 28 0 241 sec B 0 22 – 0 28 0 245 sec) the distribution of values differed somewhat One quarter of the infants in Group A as compared to more than one half of the infants in Group B had an interval of 0 25 sec or more Of the 2 premature infants in Group A with a value of 0 28 sec one had the slowest heart rate (136 beats per minute) Similarly the infant with the shortest interval had the fastest heart rate (200 beats per minute) However this known inverse correlation between length of the Q T interval and heart rate does not account for the discrepancy between the groups since the range and mean heart rates for all infants were similar

On comparison of the length of this interval in premature and full term infants respective range and means were 0 195 to 0 28 0 245 sec and 0 22 to 0 31

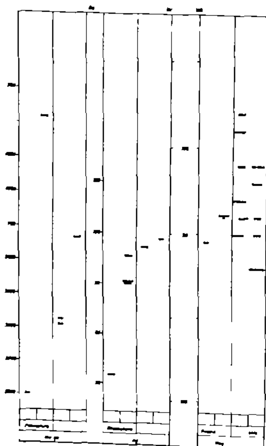


Fig 1 Age weight and heart rate in premature and full term infants Premature infants in Group A are younger than those Group B Values for weight and heart rate are similar for all

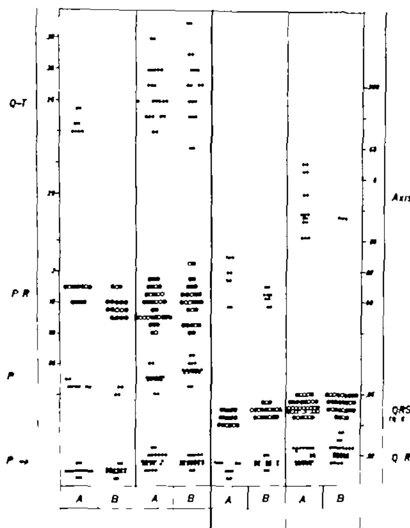


Fig 2 Distribution of cases according to duration of interval P wave amplitude and QRS axis Older infants (premature) had shorter Q R QRS and Q T intervals lower amplitude P waves and almost all have an axis of 90 degrees or less

0 268 sec Values of 0 24 sec ≤ and of 0 27 sec ≥ were present in 18 (48 6 per cent) and 5 (13 5 per cent) of the premature infants and in 7 (10 3 per cent) and 39 (57 3 per cent) of the full term infants None of the premature infants had an interval of 0 285 sec ≥ whereas 10 full term infants did have (14 7 per cent) ($p < 0005$)

Axis Eleven (65 per cent) premature infants in Group A had an axis of 75 degrees ≥ as compared with 4 (20 per cent) in Group B When both groups were combined practically all premature infants had an axis of 90 degrees ≤ Of 7 infants (19 4 per cent) exceeding this value only one had an axis of more than 120 degrees This infant was 3 months old at the time of recording and had no apparent electrocardiographic or other change apart from a transient wandering pacemaker in two leads On the other hand all full term infants had an axis of 90 degrees ≥ and 42 (61 7 per cent) had an axis of 120 degrees ≥ ($p < 0005$)

P WAVE AMPLITUDE

Lead II The weight groups were combined since no differences were noted P wave amplitude varied from *0 5 to 2 5* mm (0 25 mV) with a mean of 1 15 mm (115 mV) in premature infants and from slight to 3 0 mm (30 mV) with a

mean of 1 47 mm (147 mV) in full term infants Lower values predominated in premature infants and higher values in full term infants—1 mm ⌐ 25 premature (67 5 per cent) 10 full term (28 per cent) 1 5 mm ⌐ 12 premature (32 5 per cent) 49 full term (72 per cent) (Table I Fig 2) ($p < 0005$)

Ventricular deflections

PRECORDIALS—LEAD V_1 The weight groups were combined for analysis since the distribution was similar A Q wave was present in no premature infant but in one full term infant in Group A (0 05 mV) R waves of lower amplitude occurred in more premature than in full term infants The range and means for premature infants were 3 5 to 22 5 mm 11 05 mm as compared to 7 to 29 0 mm 18 30 mm for full term infants Values of 10 mm ⌐ (1 0 mV) and 16 mm ⌐ (1 6 mV) were present in 21 (58 3 per cent) and 6 (16 per cent) premature infants as compared to 3 (4 4 per cent) and 46 (67 6 per cent) full term infants ($p < 0005$) Only 1 premature infant had an R wave of 21 mm ⌐ (2 1

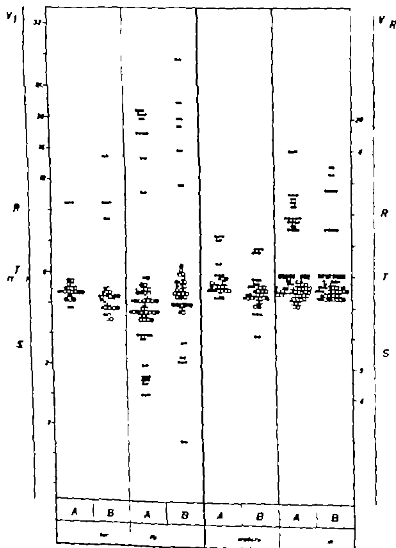


Fig 3 Amplitudes of R S and T waves in Lead V and V Older infants (premature) have lower amplitude R and higher amplitude S waves in Lead V whereas they have lower amplitude R and S waves in Lead V

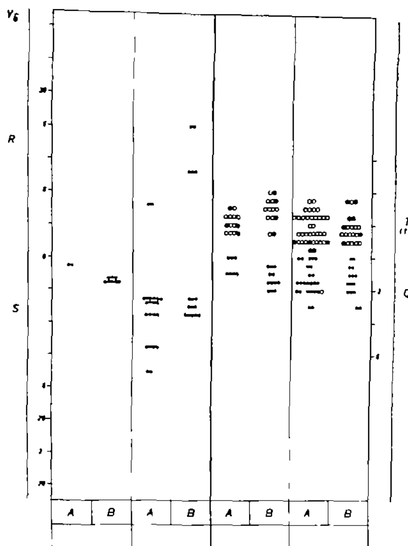


Fig. 4. Amplitudes of Q, R, S, and T waves in Lead V_6. Older infants (premature) have higher amplitude R and T waves and lower amplitude S waves.

mV.) as compared to 21 full-term infants (30.8 per cent). Similarly, S waves of lower amplitude were observed in premature infants. Values of 5 mm. ≤ and 11 mm. ≥ were present in 18 (51.4 per cent) and 7 (20 per cent) premature infants as compared to 9 (13.2 per cent) and 36 (52.9 per cent) full-term infants ($p < 0.005$). These values ranged from 0 to 24.0 mm. (mean 6.72 mm.) in premature infants and from 0.5 to 26.5 mm. (mean 11.37 mm.) in full-term infants.

LEAD V_{4R}. A Q wave was present in 2 premature infants in Group A (0.5 to 2.0 mm.), 3 full-term infants in Group A and 2 in Group B (slight to 1.0 mm.). As in the case of Lead V_1, R waves of lower amplitude were present in premature infants. Amplitudes of 5.0 mm. ≤ (0.5 mV.) and 5.5 mm. ≥ were present in 24 (66.6 per cent) and 12 premature infants, of which only 1 was 10.5 mm. ≥ (2.78 per cent), as compared to 2 (2.9 per cent) and 66 full-term infants, of which 29 were more than 10.5 mm. (42.6 per cent) ($p < 0.005$). The single high value among premature infants was present in a 107-day-old female infant in Group B who also had the highest R wave in Lead V, second highest in Lead V_1, third lowest R and lowest T waves in Lead V_4 and the deepest S wave in Leads V_{4R} and V_1. On the other hand, a greater number of S waves of higher amplitude were present in premature

infants and of lower amplitudes in full term infants Values of 3 5 mm and 0 5 mm were present in 10 (27 8 per cent) and 9 (25 per cent) premature infants and 4 (5 9 per cent) and 43 (63 2 per cent) full term infants (range and means 0 5 to 13 0 mm 2 77 mm premature 0 5 to 6 0 mm 0 89 mm full term (Table II Fig 3) ($p < 0005$)

LEAD V[illegible] A Q wave was present in 1 premature infant in Group A (0 5 mm) 7 full term infants in Group A and 3 in Group B (slight to 1 5 mm) The distribution and mean R wave amplitudes were similar for both premature and full term infants regardless of weight group (means 18 3 mm premature 19 2 mm full term) S waves ranged from 1 0 to 26 0 mm with a mean of 11 14 mm in premature infants and from 0 to 16 0 mm with a mean of 7 76 mm in full term infants As in the case of Lead V[illegible] S waves were higher in premature and lower in full term infants Values of 14 5 mm and 8 0 mm were present in 7 (19 4 per cent) and 14 (39 per cent) premature infants and in 2 (3 3 per cent) and 43 (65 per cent) full term infants ($p < 01$)

LEAD V[illegible] The incidence and distrubution of Q waves was similar for both groups regardless of weight The R waves present in premature infants were of higher amplitude than those in full term infants Eleven (30 5 per cent none below 5 0 mm) and 25 (69 5 per cent) premature infants as compared to 42 (61 7 per cent with one fourth of the cases 5 0 mm or less) and 26 (38 3 per cent) full term infants had values

Table II Mean amplitude of Q R S and T waves in premature and full term infants of similar weight

	Premature 36	Full term 68		Premature 36	Full term 68
Lead V[illegible]			Lead V[illegible]		66
Q	[2]	[4] 0515	Q	[1]	[10] 1136
R	4 74 (2 216)	9 92 (3 364)	R	18 33 (6 ?28)	66 19 ?2 (5 431)
S	2 78 (2 676)	0 90 (1 305)	S	11 14 (6 073)	66 7 77 (3 377)
T	2 16 (0 964)	2 18 (0 978)	T	2 70 (1 824)	67 2 17 (1 873)
Lead V[illegible]			Lead V[illegible]		
Q	[0]	[1]	Q	[32] 1 85 (1 392)	[54] 1 53 (1 256)
R	11 06 (4 759)	18 31 (5 024)	R	13 46 (4 451)	9 47 (6 403)
S	6 72 (5 337)	11 38 (5 528)	S	3 32 (2 473)	8 35 (5 078)
T	3 70 (1 513)	67 3 18 (? 416)	T	2 79 (1 361)	1 91 (1 05)

[illegible] 1/10 mV [illegible]
$p < 001$

of 10.5 mm ≤ and 11.0 mm ≥ respectively (p < .01). Mean values also reflected this trend: 13.76 mm. in premature and 9.48 mm. in full-term infants. On the other hand, S waves of lower amplitude were found in premature infants with mean and maximum values of 3.32 and 9.5 mm. in premature and 8.34 and 29.0 mm. in full-term infants. Amplitudes of 4.0 mm. ≤ and 4.5 mm. ≥ were present in 28 (77.7 per cent) and 8 (maximum 9.5 mm.) premature infants and in 10 (14.7 per cent) and 58 full-term infants with 22 (32.3 per cent) cases 10 mm. ≥ (Table II, Fig. 4) (p < .0005).

T waves

PRECORDIAL LEADS. The T waves found in premature infants in Group B were of higher amplitude than those in Group A in all of the above-mentioned leads. In Lead V_4, full-term infants tended to have waves of lower amplitude, i.e., an equal number of full-term infants had values of 1.5 mm. ≤ and 2 mm. ≥, 4 of whom had a value of 4 mm. ≥ (5.8 per cent), as compared to one fourth and three fourths of the premature infants, 7 of whom were in the higher range (19.4 per cent) (p < .01).

Comment

These findings may be ascribed to differences in age, in recording technique, or to differences between electrocardiograms of full-term and premature infants. However, as stated earlier, follow-up study failed to demonstrate a typical electrocardiogram for premature infants.[1] Those differences encountered between the tracings of premature infants and the values reported for full-term infants which were recorded with different instruments, paper speeds, and electrodes were present only during the first week or two of life.

Comparison of single rather than serial values necessarily limits the conclusions which can be drawn. But if the data are interpreted as representing a continuing process of maturation in early infancy and are viewed in conjunction with previous studies of full-term infants during the first week of life,[4] it then becomes evident that all intervals are relatively longer at birth but that it is the rate of decrease in duration which differs for each. Thus, intervals which reflect atrial and atrioventricular conduction show relatively little change after the first hour of life, whereas those which involve ventricular conduction are not only influenced by events attending birth but also by those affecting the first few months of life.

Precordial leads show more right ventricular dominance in younger (full-term) infants and more left ventricular dominance in older (premature) infants, which accords with the findings of others.[7] Lead V_{4R} seemed to reflect these findings more adequately than did either Lead V_1 or Lead V. It is also of interest that T waves in Lead V_4 at the end of the first week of life are of relatively low amplitude in comparison with those in older infants. Admittedly, there is a significant disparity in size of the two groups, but the trend of the findings also accords with the view that these differences reflect electrocardiographic maturation.

The Q-R time is dependent in some measure on the relative thickness of the underlying ventricle. In a previous study a direct correlation was found between the amplitude of the respective R wave and the duration of this interval.[4] It is generally agreed that in the immediate neonatal period physiologic right ventricular dominance is present. This is replaced within 4 weeks of birth by left ventricular preponderance. The decrease with age in duration of the Q-R time in Lead V_1 may well reflect this change.

There is evidence that the length of the QRS interval is related to the weight of the ventricles.[10] However, in a previous study of these full-term infants, heart volume measured on roentgenograms of the chest decreased during the first week of life, *confirming the findings of others*,[11] but independently of the decrease in the length of the QRS and Q-T intervals.[4] This is perhaps not surprising since the Q-T interval in particular is influenced by many different factors and at this age of transition it seems likely that it is their interrelationship which determines the resultant value. Presumably by the end of the first week of life the effects of circulatory adaptation to birth are significantly reduced, but there is also the question whether loss of the placenta and subsequent closure of the ductus result in a significant

decrease in cardiac work with subsequent further reduction in heart size

Similar decreases in the duration of the QRS and Q T intervals during early infancy have also been observed by Ziegler in full term infants He attributed the decrease in QRS interval to a concomitant increase in heart rate However the changes in length of this interval with rate appear to be minimal and probably do not exceed 0 007 sec for a change in rate as large as 60 beats per minute Furthermore in his study of the Q T index which takes account of changes in heart rate a similar decrease occurred

On the other hand Wachtel and associates[11] in a serial study of full term infants during their first 3 months of life did not detect a significant change in the length of the QRS interval But it is not clear whether all measurements were made by the same individual a fast paper speed (25 mm per second) was used which limits accuracy of measurement of intervals especially with the rapid heart rates of infancy and follow up was poor since only 31 of the 50 patients were re examined

Previous serial investigation of these full term infants showed a highly significant decrease in the length of the Q T interval especially from the third to the fifth or sixth days of life[5] This change was attributed to a decrease in diastolic overload of the left ventricle as the degree of left to-right shunting across the ductus arteriosus presumably became insignificant Although the hemoglobin was determined in only 19 of these premature infants at the same time that the electrocardiogram was recorded scattergrams suggested a relation hip between lower hemoglobin values and longer intervals All 7 infants with an interval of 0 255 sec or more had a hemoglobin of 10 Gm or less whereas none with a higher value had an interval in this range When the interval was corrected for heart rate using Bazett s formula a Q T index of 0 40 sec was present in 6 infants with a hemoglobin of 10 Gm or less as compared to 1 infant with a hemoglobin level above this In premature infants physiologic anemia occurs earlier and is more severe[14 15] Therefore the effects of anemia are probably accentuated in this study On the other hand electrocardiographic changes ascribable to anemia are diverse and nonspecific Although any explanation can only be speculative it seems feasible that a further decrease in the length of this interval after the first week of life possibly resulting from a reduction in cardiac work may be counterbalanced to some extent by physiologic anemia with its associated tendency to prolong this interval Subsequent improvement in anemia may then be followed by a further decrease in the length of this interval providing that this occurs before significant growth of the heart leads to an increase in the length of the interval with age

Conclusion

Electrocardiograms of 68 healthy full term and 37 healthy premature infants of similar weight but with a mean age of 136 hours and 69 days respectively are compared

Relatively longer P R QRS and Q T intervals and evidence of more right ventricular dominance are present in tracings of full term infants whereas relatively shorter intervals and evidence of more left ventricular dominance are present in tracings of premature infants

Possible explanations for these findings are discussed

The advice and encouragement of Prof John Lind and the help of Miss Siv Lundqvist who cheerfully and carefully assisted with various aspects of this study are gratefully acknowledged

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Cardiac and renal hyperresponsiveness to acute plasma volume expansion in hypertension

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Essential hypertension has long been considered to be a disorder of pressure regulating mechanisms neurogenic and humoral Recent studies many of which were summarized in the Proceedings of the Prague Symposium[1] have shown that these classifications are not mutually exclusive but often overlap since neural mechanisms often operate through humoral mediation whereas humoral substances may have profound effects on central and peripheral neural function In particular a hypothesis has been advanced by Fries in his review of circulatory regulation

Let us suggest that the basic mechanism in hypertension may be a disorder of the capacity vessels and limitation of their ability to respond adequately to sharp increases in plasma volume It has previously been observed by several authors[2-11] that hypertensive patients characteristically respond to infusions of body fluid expanding solutions by greater natriuresis than do normotensive subjects However these workers had limited their consideration primarily to renal responses in terms of flow of urine and output of sodium or chloride neglecting the possibility that these might be determined by responses of the heart to its regulatory mechanisms and the circulation as a whole[14] Indeed several workers suggested that the primary defect might lay in a specific change in renal sodium transport systems

The present study describes responses of cardiac output (C O) and total peripheral resistance as well as renal responses to expansions of plasma volume and body fluid produced by infusions of either saline rich aqueous solution or iso oncotic iso osmotic dextran in control normotensive subjects and in patients with essential hypertension The data strongly suggest that the defect in hypertensive patients which establishes the excessive natriuretic response to volume expansion is determined by the cardiac response to volume expansion They also suggest a possible defect in cardiac regulatory mechanisms and in particular in the mechanisms which control the adaptation of capacitance vessels to volume expansion

Procedures

The study was done on 26 subjects of whom 11 were normotensive with negative family history of hypertension and 15 had apparent essential hypertension The first series of observations included 5 control as well as 8 hypertensive subjects Among

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Table IA General data of persons investigated (First group of observations—saline)

Number	Name	Sex	Age	Weight (Kg)	Body surface area (M²)	B P (mm Hg)	Diagnosis	Probable duration of hypertension (yr)
1	S V	M	34	68	1 85	125/80	Peptic ulcer	—
2	Se K	F	33	64	1 74	125/80	St p varicotomiam	—
3	S J	M	53	55	1 61	135/80	Achlorhydria	—
4	Su K	M	20	72	1 83	130/90	Orthostatic proteinuria	—
5	R H	F	21	79	1 87	115/	St p varicotomiam	—
♦	N (1–5)		32 ?	67 6	1 78			
6	N R	F	50	60	1 66	175/98	Essential hypertension I Bronchitis chronica	3
7	K K	F	27	91	1 99	150/95	Essential hypertension I Cholecystopathia	1
8	S F	F	55	63	1 62	190/107	Essential hypertension I	6
9	Z M	F	48	55	1 47	225/120	Essential hypertension I	1
10	Z V	M	49	76	1 88	230/110	Essential hypertension II Peptic ulcer	5
11	M Z	F	51	74	1 83	230/120	Essential hypertension II	9
12	P E	F	51	82	1 84	260/130	Essential hypertension II Varices cruris bilat	8
13	B M	F	57	67	1 76	205/108	Essential hypertension II	2
♦	H (6–13)		48 5	71 0	1 77			
	N × H							
	t		2 677	0 542	0 286			
	p		< 0 05	n	n			

the 8 hypertensive subjects were 4 in Stage I and 4 in Stage II of the disease by the WHO classification The second series of observations included 6 normotensive and 7 hypertensive subjects Among the latter 5 were in Stage I of the disease and 2 in Stage II The general data on the subjects are listed in Tables IA and IB No patient showed any signs of renal or cardiac damage or anemia

All patients were investigated after they had been without food and water for 14 hours and the hypertensive patients had received no drug for at least 10 days previously Investigations were carried out with the subjects in the recumbent position in a quiet laboratory and all experiments started between 7 and 8 A M A catheter was introduced into the bladder (in males only after surface anesthesia of the urethra) and then plastic catheters were inserted into the brachial artery and antecubital vein percutaneously[17,18] for injection of dye sampling of blood measurement of blood pressure and infusions In a second series of experiments the venous catheter was introduced up to the subclavian vein or superior vena cava without x-ray control for registration of central venous pressure (C V P)

After introduction of the catheters we waited until the rate of flow of urine was constant and only then were the various parameters measured at least twice in all observations The above mentioned values were considered to be resting values The infusion was then started In the first group of observations 500 ml of 5 per cent NaCl solution was administered In the second group 6 per cent of iso oncotic dextran in isotonic NaCl in an amount of 1 200 ml per 70 Kg of body weight was given In all instances the infusion lasted 55 to 60 minutes All the aforementioned parameters were measured twice during the infusion and after termination of the infusion in each clearance period All measurements were continued until it

was obvious that the diuresis had reached its maximum and had begun to decrease

Cardiac output was measured by means of Coomassie blue dilution[19,20] in the first series using an ear oximeter and in the second by means of a flow cuvette. Both were attached to the Cambridge dye dilution recorder. The curves were calibrated by means of the end tail method and the calculations were made according to Hamilton and associates [1] as modified by Cyvin[2]. Blood pressure in the first series was estimated by auscultation and mean pressure was taken as diastolic + 40 per cent of pressure amplitude according to Brod and associates[3]. In the second series of experiments the pressure was measured with a Statham P23Db pressure transducer attached to the Hellige electromanometer. Mean pressure was estimated by means of an electrical integrator. All curves were recorded on a Hellige Multiscriptor. Central venous pressure was measured by the same apparatus in 9 of the subjects in the second group. The phlebostatic level was taken according to Winsor and Burch[21]. The concentrations of inulin in the plasma and urine in the first group were determined by Harrison's modification[2]; in the second group endogenous creatinine concentrations were estimated by the method of Brod and Sirota[24]

Table 1B General data of persons investigated (Second group of observations—dextran)

Number	Name	Sex	Age	Weight (kg)	Body surface area (M²)	B P (mm Hg)	Diagnosis	Probable duration of hypertension (yr)
1	N L	F	39	60	1.65	110/70	St p ancotomiam	—
2	C N	F	47	74	1.81	110/75	St p an otomiam	—
3	S J	M	32	68	1.77	125/75	Thrombang ti obliteran incip	—
4	N N	M	47	57	1.67	170/80	Atherosclerosis extr inf incip	—
5	B M	F	37	64	1.72	120/80	St p ancotomi tr	—
6	G M	F	44	76	1.81	120/80	Varices crurni bilat	—
♦	N (1–6)		40.2	66.5	1.73			
7	K N	M	38	86	2.03	145/100	Essential hypertension I	1
8	L N	M	46	64	1.76	175/103	Essential hypertension I Atherosclerosis extr inf incip	
9	T K	F	61	59	1.58	170/95	Essential hypertension I	1½
10	S N	F	35	63	1.67	155/95	Essential hypertension I Psychoneurosis	10
11	F N	F	49	72	1 9	178/95	Essential hypertension I	1
1	R B	M	55	0	1.85	175/105	Essential hypertension II Bronchitis chronica	5
13	F J	M	48	71	1.86	173/110	Essential hypertension II	3
♦	H (7–13)		50.3	69.3	1.80			
N × H								
t			2.509	0.60	0.95			
p			< 0.05	n	n			
♦	Nt		36.(	(0	1.75			
♦	Ht		49.3	0 ?	1.78			
Nt × Ht								
t			3.40	0.8??	0.4 3			
p			< 0.01	n	n			

Infusion of inulin was given via a pressure pump at a constant rate of 0.2 ml. per minute. Estimations of sodium and potassium were done by a single-ended Zeiss flame photometer. Samples of blood for the determination of plasma levels of Na and inulin were taken when C.O. was estimated. Urine was collected with a rubber catheter from the bladder, which was washed out between collection periods. The shortest interval between collections was 15 minutes. Stroke volume (SV) was calculated by dividing C.O. by pulse rate as registered from the records of blood pressure. Total peripheral resistance was calculated in terms of mean pressure in the brachial artery divided by C.O., and was expressed in arbitrary units. Glomerular filtration rate (GFR) and the excreted amount of sodium ($U_{Na}V$) and potassium (U_KV) were calculated in the usual manner, and the tubular rejection fraction of sodium (RF_{Na}) was taken as the amount of excreted sodium load divided by the filtered sodium load.

Statistical evaluations were carried out by means of the usual Fisher t test, and correlations were evaluated in terms of correlation coefficients.

Results

Since statistical analysis of changes in arterial pressure established that there were no significant differences between control and hypertensive subjects during either series of infusions of saline or dextran, these data are not listed.

Primary hemodynamic and renal changes induced by saline are listed in Tables IIA and IIB; those induced by dextran are given in Tables IIIA and IIIB.

Fig. 1 shows the association of maximum relative changes in C.O. and $U_{Na}V$ induced by saline in normotensive and hypertensive subjects. As anticipated, changes in $U_{Na}V$ are greater in hypertensive than in normotensive subjects, and the data establish an association between this function and C.O. Fig. 2 demonstrates similar findings with dextran, which yield an even

Table IIA. Hemodynamic effects of infusions of hypertonic saline

Number	Name	Mean arterial pressure (mm. Hg) a	Cardiac output (ml./min.) a	b		Total peripheral resistance (arbitrary units) a	b	c
1	S N	95	5 996	+1 485	+24 8	15 8	− 2 6	−16 5
2	S K	97	7 203	+2 274	+31 6	13 5	− 2 5	−18 5
3	S J	100	6 361	−0 313	− 4 9	15 6	+ 1 4	+ 9 0
4	Sa K	106	7 676	+3 175	+41 6	14 2	− 3 8	−26 8
5	R H	—	5 868	+2 751	+46 9	—	—	—
ϕ	N (1-5)	99 5	6 611	+1 874	+28 0	14 8	− 1 9	−13 2
6	N R	111	4 883	+5 567	+114 0	23 1	−12 0	−51 9
7	K K	114	7 265	+6 114	+ 84 2	15 7	− 6 8	−43 3
8	S I	123	5 214	+3 681	+ 70 7	23 5	− 9 9	−42 1
9	Z M	146	6 374	+4 539	+ 71 2	23 6	−11 0	−46 6
10	Z N	162	7 481	+4 498	+ 60 1	22 0	− 7 7	−35 0
11	M Z	168	5 513	+3 931	+ 71 3	30 6	−13 2	−43 1
12	L E	174	5 710	+5 805	+101 7	30 5	−15 5	−50 8
13	B M	140	—	—	—	—	—	—
ϕ	H (6-13)	143 0	6 063	+4 877	+ 81 9	4 1	−10 9	−44 7
	N × H t	4 48	1 01	4 497	4 658	4 751	5 104	3 417
	p	< 0 01	n	< 0 005	< 0 001	< 0 005	< 0 001	< 0 05

Means of resting values. b Maximum [illegible] in absolute units. Maximum changes of [illegible] in percent [illegible].

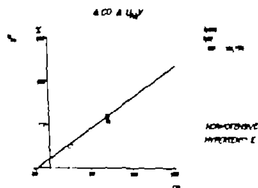


Fig. 1 Correlation between maximal changes in cardiac output (Δ C O) and maximal changes in urinary sodium output (Δ U$_{Na}$ V) after infusion of 500 mL of 5 per cent NaCl solution. Both parameters are expressed as percentile changes of resting values

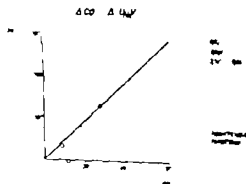


Fig. 2 Correlation between maximal changes in cardiac output (Δ C O) and maximal changes in urinary sodium output (Δ U$_{Na}$ V) after infusion of 1 700 ml of iso-oncotic isotonic dextran solution. Both parameters are expressed as percentile changes of resting values

closer association of functions. Similar correlations were demonstrated between maximal changes in C O and flow of urine (for saline series $r = 0.823$, $p < 0.01$, $y = 5.731 X - 4.481$ and for dextran series $r = 0.722$, $p < 0.01$, $y = 7.199 X - 7.445$). Fig. 3 shows the association between maximal changes in C O and C V P in 9 subjects, 4 of whom were hypertensive, as affected by infusions of dextran. Increments in C V P were greater in hypertensive than in normotensive subjects but the difference was not significant, very probably only because of the small number of measurements.

Data from saline and dextran experiments in both series are summarized in Fig. 4 with reference to resting (under the conditions of investigation) mean arterial pressure and changes in C O. This demonstrates that increments in C O induced by volume expansion are smaller in normotensive than in hypertensive subjects. The responses of C O were unusually great in patients with the mildest hypertension whose mean blood pressure during the investigation was less than 115.0 mm Hg. In the remainder of the hypertensive subjects the maximal response of C O to infusion was roughly proportional

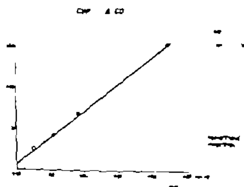


Fig. 3 Correlation between maximal changes in central venous pressure (Δ C V P) and maximal changes in cardiac output (Δ C O) after infusion of 1 700 ml of iso-oncotic isotonic dextran solution. Changes in C V P are expressed in millimeters of mercury and changes in C O are given as percentages of resting values

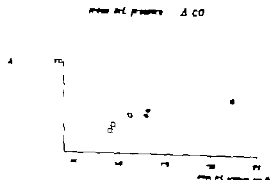


Fig. 4 Relation between level of resting mean blood pressure and maximal changes in cardiac output (Δ C O) after both saline and dextran infusions. Open symbol = normotensive subjects and solid symbol = hypertensive subjects. Squares = hypertonic saline infusion experiments. Circle = iso-oncotic isotonic dextran infusion experiments.

Table IIB Renal effects of infusions of hypertonic saline

Number	Name	G F R (ml/min)			V/min (ml/min)		
		a	b	c	a	b	c
1	S V	111 5	+25 5	+22 9	0 9	+ 1 91	+241 8
2	S K	118 1	+15 4	+13 0	1 41	+ 3 06	+217 0
3	S J	109 6	+ 9 2	+ 8 4	1 88	+ 0 72	+ 38 3
4	Su K	148 6	+36 9	+24 8	0 97	+ 0 85	+ 92 4
5	R H	153 0	+31 7	+20 7	0 95	+ 0 33	+ 34 7
φ	N (1–5)	128 2	+23 7	+18 0	1 19	+ 1 37	+124 8
6	V R	78 1	+18 6	+23 8	1 42	+10 51	+740 1
7	K K	139 9	+37 9	+23 5	0 56	+ 3 04	+542 9
8	S F	85 2	+13 1	+15 4	1 12	+ 5 16	+460 7
9	Z M	107 5	+ 0 8	+ 0 7	1 42	+ 4 99	+351 4
10	Z V	115 6	+ 1 7	+ 1 5	2 20	+ 6 67	+301 2
11	M Z	131 0	+27 1	+20 7	1 80	+10 69	+593 9
12	P E	110 8	+21 1	+19 0	1 76	+ 7 62	+433 0
13	B M	102 3	+ 0 4	+ 0 4	1 77	+ 3 68	+207 9
φ	H (6–13)	108 8	+14 5	+13 1	1 51	+ 6 54	+454 1
	N × H						
	t	1 674	1 337	0 907	1 145	4 209	3 891
	p		n	n	n	< 0 01	< 0 01

G F R [illegible]

to the height of the mean resting blood pressure

Comment

As noted briefly above many observers have demonstrated that hypertensive subjects frequently respond to intravenous fluid loads by larger increments in Na output than do normotensive subjects Some have associated this with a possible paradoxical renal tubular response to sudden fluid excess It is paradoxical because others such as Perera and Blood [11] Thomas [9] Dahl and associates [18] have shown that it is a common characteristic of hypertensive and prehypertensive subjects to show delayed elimination of Na during long periods not only when the intake of sodium is restricted but also when it is normal or increased This last phenomenon has been clarified to a certain degree by new observations that suggest at least a secondary participation of aldosterone in the mechanism that supports blood pressure in many hypertensive patients [n n] The present data resolve this paradox since they indicate that the renal response is associated with and presumably is caused directly by a larger increment in C O in hypertensive than in normotensive subjects Such a hemodynamically dominated transient response may well obscure any relatively small humoral influences on renal reabsorption of Na due to hormonal influence or other smaller influences

As indicated above the response of C O to volume expansion is much more regular when the agent used is dextran rather than saline This further supports the concept that the C O and ultimately the renal response to dextran or saline is a sequel to an increment in plasma volume since it is well known that saline rather promptly diffuses into body fluid whereas dextran remains in the circulating blood for a long period and more effectively increases and sustains an increment in plasma volume

In brief it seems that the abnormal

U V (μeq/min)			RF (%)			C_{Na}V (μeq/min)			P_{Na} (meq/L)	
a	b	c	a	b	c	a	b	c	a	b
208	+0 533	+ 256 3	1 43	+ 2 35	+164 3	67	+ 98	+146 3	131 0	+11 9
186	+1 005	+ 540 3	1 14	+ 5 02	+440 4	46	+ 6	+145 7	135 ?	+ 7 0
350	+0 407	+ 114 9	2 34	+ 1 91	+ 84 6	88	+ 37	+ 42 0	136 5	+12 4
173	+0 344	+ 198 8	0 87	+ 1 08	+124 1	68	− 3	− 4	135 1	+ 7 9
145	+0 198	+ 136 6	0 72	+ 0 65	+ 90 3	51	+ 21	+ 41 2	137 3	+16
212	+0 496	+ 249 5	1 30	+ 2 70	+190 1	64	+ 44	+ 136	134 6	+11 1
230	+2 313	+1005 7	2 23	+16 36	+733 6	49	+166	+335 8	137 0	+ 9 5
144	+0 883	+ 613 2	0 79	+ 3 46	+438 0	50	+ 50	+100 0	131 0	+ 9 0
114	+1 378	+1 088	0 98	+ 9 20	+935 8	56	+ 41	+ 73 2	136 4	+11 4
191	+1 147	+ 597 9	1 28	+ 6 72	+525 0	38	+107	+265 1	134 9	+14 9
375	+1 575	+ 4 0 0	2 20	+ 8 85	+407 3	52	+100	+192 3	148 2	+ 2 3
410	+2 22	+ 543 2	2 23	+ 9 06	+406 3	27	+ 67	+229 6	140 5	+ 7 0
337	+1 930	+ 572 7	13	+ 9 31	+437 1	75	+ 45	+ 60 0	143 9	+ 6 2
207	+1 183	+ 572 5	1 43	+ 7 60	+531 5	11	+ 33	+300 0	147 1	+ 8 0
231	+1 579	+ 691 8	1 66	+ 8 82	+551 6	45	+ 75	+195 3	139 1	+ 8 5
0 67	4 123	3 259	1 016	4 098	3 692	1 833	1 266	2 745	1 690	1 198
n	< 0 01	< 0 01	n	< 0 01	< 0 01	n	n	< 0 05	n	n

LaV P ... P ... b and ... n Table II A

natriuretic response of the hypertensive subject is a sequel to increased C O and that this follows an increased C V P although observations on C V P were not made in all cases. It seems that the increment in C V P is due to expansion of plasma volume. The question then arises why an increment in plasma volume should have a larger effect in hypertensive than in normotensive subjects. Thus the present data support Frei's hypothesis[2] of a diminished distensibility of capacity vessels in essential hypertension and accord with experimental data of Floyer[4] and Ledingham and Cohen[28] on the mechanisms of renal hypertension in rats.

It is a familiar observation that intact subjects both human and canine do not respond to increments in volume or to increments in C V P with the proportionate increments in C O which characterize subjects with denervated hearts[14] (or the heart lung preparation[17]) i e that Starling's law is valid only in abnormal situations. This dissociation is attributed to hemostatic responses by cardiac nerves which damp an underlying but normally transient Starling's response.[18,19] The present data which concern only maxima of responses demonstrate that even the normotensive subject shows some association between volume expansion and C O response. They demonstrate this quite conspicuously as a characteristic of the hypertensive subject. Such observations suggest that cardiac regulatory or modulating neural function is diminished in hypertensive patients. This concept would accord with the frequent observation that pressor responsiveness to an agent such as noradrenalin or angiotensin as well as depressor responsiveness to an agent such as histamine are often augmented in hypertensive patients. It is tempting to associate this diminished response of the hypertensive neural mechanism with the altered function of baroreceptors found in renal hypertensive dogs by McC

Table IIIA Hemodynamic effects of infusions of iso oncotic dextran

Number	Name	Mean arterial pressure (mm Hg) a	C V P (mm Hg) a	C V P (mm Hg) b	C O (ml/min) a	C O (ml/min) b	C O (ml/min) c
1	N I	76 5	1 6	+4 5	7 100	+0 580	+ 8 1
2	C V	93 2	4 6	+6 6	7 450	+2 200	+29 5
3	S J	94 2	—	—	7 774	+0 920	+11 9
4	V V	98 3	2 0	+1 5	7 391	+1 177	+15 9
5	B M	98 9	5 0	+5 4	7 000	+1 890	+27 0
6	G M	106 1	5 1	+5 1	10 714	+2 785	+25 9
ϕ	N (1–6)	94 5	3 7	+5 2	7 905	+1 592	+19 7
7	K V	109 8	3 8	+8 4	6 815	+6 204	+91 0
8	L V	115 2	1 4	+5 8	7 810	+3 247	+41 6
9	T K	[illegible]	—	—	4 672	+2 223	+48 0
10	S V	121 5	—	—	7 192	+2 852	+39 7
11	F V	129 3	—	—	6 725	+2 722	+40 5
12	R B	137 8	2 3	+5 9	7 004	+4 393	+62 7
13	E J	150 5	5 1	+7 0	5 706	+3 817	+73 3
ϕ	H (7–13)	125 0	3 3	+6 8	6 482	+3 637	+56 3
	N × H						
	t	4 491	0 378	2 263	2 020	3 220	3 985
	p	< 0 001	n	n	n	< 0 01	< 0 01

C O C d output S V % … T P R Total peripheral resistance C V P C … p … Table

Green and Page[46] although their data establish only resetting with regard to the level of pressure and the persistence of nearly normal modulatory baroreceptor function. Integrity of modulatory cardio-acceleratory function is shown by the similarity of pulse rate responses in hypertensive and control subjects.

Summary and conclusions

Diuretic and natriuretic responses to intravenous hypertonic NaCl loads and to infusions of iso-oncotic isotonic dextran were compared in 26 subjects: 11 normotensive and 15 hypertensive (Grades I and II) during concurrent measurement of cardiac output, pulse rate, and arterial pressure.

Maximal changes in natriuresis and cardiac output after both types of infusions were found to be significantly greater in hypertensive than in normotensive subjects. Statistically significant correlations were found between maximal changes in central venous pressure and in cardiac output, and between maximal changes in cardiac output and in sodium excretion.

It is suggested that exaggerated natriuresis in hypertensive patients may be associated directly with the excessive response of cardiac output. The latter could be attributable to an increase in plasma volume which is more regular in those who are given dextran.

The cardiac data suggest a defect in the modulatory function of cardiac innervation in hypertension. They strongly indicate, as had been suggested for man and described in rats, that hypertension is associated with deficient ability of capacity vessels to dilate in response to sudden increments in plasma volume.

The two phenomena are not clearly associated etiologically. The defect in innervation may be secondary, as has been shown for pressure regulation in dogs

Pulse rate			*S 1 (ml)*			*T P R (arbitrary units)*		
a	*b*	*c*	*a*	*b*	*c*	*a*	*b*	*c*
69 0	+11 0	+15 9	103 0	+11 5	+11 2	10 7	+ 0	+ 1 4
77 5	+ 3 5	+ 7 6	103 3	+27 1	+21 4	12 5	− 2 4	−19 2
76 0	+13 0	+17 1	10 0	+ 0 2	+ 0 2	12 1	− 1 0	− 8 3
69 0	+ 8 0	+11 6	105 5	+ 3 6	+ 3 4	13 3	− 1 4	−10 5
67 8	+12 2	+19 4	111 8	+ 6 6	+ 5 9	14	− 3 ?	−22 5
81 5	+16 5	+20 2	131	+ 6 8	+ 5 2	10 0	− 2 5	−14 0
71 8	+11 0	+15 3	109 5	+ 8 5	+ 7 9	12 1	− 1 7	−1? 2
75 0	+17 0	+27 7	97 0	+49 3	+53 6	16 3	− 8 2	−50 3
69 0	+ 8 0	+11 6	114 7	+36 7	+32 0	14 7	− 4 4	−29 9
48 0	+ 9 0	+18 8	96 7	+39 9	+41 3	24 9	− 7 5	−50 1
66 5	+28 5	+47 9	108 2	+13 0	+12 0	16 9	− 4 9	−29 9
75 0	+23 0	+30 7	90 3	+ 9 1	+10 1	19 7	− 6 6	−33 5
65 5	+14 5	+22 1	107 0	+35 5	+33 2	19 0	− 6 8	−32 6
65 0	+11 0	+16 7	76 4	+41 1	+53 8	29 8	−12 3	−42 1
66 7	+15 9	+23 6	97 9	+37 1	+33 7	20 2	− 7 2	−35 4
1 143	1 361	1 737	1 695	3 353	3 442	3 507	4 600	5 083
n	n	n	n	< 0 01	< 0 01	< 0 01	< 0 01	< 0 001

[illegible] —[illegible] val a b—Maximal change after infusion absolute units c—Maximal change after infusion in percentages

whereas studies in rats indicate the capacity defect as an early mechanism It is unlikely that they are wholly independent

The data indicate that diuretic and natriuretic responses to salt or volume loads in hypertension are more probably circulatory in origin than dependent on a paradoxical response in cellular mechanisms of tubular exchange of Na

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Table IIIB K nal effects of infusions of iso oncotic dextran

N mber Name		C F R (ml /min)		V /min (ml /min)		
		b	c	a	b	c
1 N I	80 4	+21 1	+270	1 55	+ 2 44	+157 4
2 C N	101 1	+21 9	+ 1 6	0 86	+ 4 75	+552 5
3 S J	134 8	+ 5 6	+ 4	1 13	+ 0 62	+ 54 9
4 N N	95 6	+11 1	+11 6	1 86	− 0 41	− 22 0
5 B M	120 2	+ 7 9	+ 3 1	0 64	+ 1 26	+196 9
6 C M	96 4	+13 4	+13 9	1 71	+ 1 57	+ 91 8
ø N (1 6)	104 2	+16 9	+16 9	1 22	+ 1 0	+171 9
K N	110 4	+31 8	+28 9	1 10	+10 01	+910 0
8 I N	160 4	+30 0	+18 7	0 88	+ 1 64	+186 4
9 I K	82 4	+23 9	+22 0	1 35	+ 4 44	+378 9
10 S N	97 4	+16 5	+16 9	1 54	+ 5 2	+371 4
11 F N	92	+45 7	+49 3	1 42	+ 2 05	+144 4
12 R B	119 5	+40 0	+33 5	1 05	+ 3 62	+344 8
13 E J	120 7	+16 1	+13 3	1 84	+ 3 01	+272 3
♦ H (7 13)	111 9	+29 1	+27 1	1 31	+ 4 64	+365 5
N × H						
t	0 548	2 195	1 07	0 058	21	1 500
P	n	n	n	n	< 0 05	n

G F R Cl [illegible] (K) Ott [illegible] T II IIA and IIB

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$U_{Na}V$ (µEq/min)			RF (%)			U_KV (µEq/min)			P (mEq/L)	
a	b	c	a	b	c	a	b	c	a	b
46	+40	+16.3	2.31	−0.12	−5.?	49	+48	+98.0	141.5	−1.75
159	+171	+81.1	1.17	+0.82	+100	94	+13	+13.8	134.0	−2.00
244	+78	+32.0	1.78	+0.42	+32.8	0	+6	+8.6	142.0	−4.0
290	−7	−2.5	2.7?	−0.47	−21.?	7?	−30	−39.0	142.0	+4.00
1?9	+260	+145.2	1.03	+1.97	+191.3	4?	+75	+59.5	143.0	−1.5
254	+191	+72.5	1.9?	+1.22	+67.0	85	+42	+49.4	136.8	−1.5
2?	+114	+57.9	1.64	+0.64	+55.8	0	+17	+31.7	139.9	−0.82
213	+519	+25?.7	1.41	+2.90	+205	34	+26	+76.5	136.8	−1.5
199	+357	+1?9.4	0.84	+1.61	+191.?	—	—	—	14?.0	+1.50
289	+79	+10?.1	2.43	+2.00	+87.3	4	+1?	+8.6	143.4	+2.20
351	+461	+130.?	2.54	+2.45	+96.5	—	—	—	143.3	0.00
311	+396	+127.3	2.3?	+1.1?	+48.3	25	+10	+40.0	144.5	+1.00
199	+416	+209.0	1.43	+2.05	+133.4	28	+24	+85.7	145.0	+3.50
250	+605	+242.0	1.44	+3.01	+209.0	63	−14	−2?	143.8	+0.75
259	+440	+178.?	1.?7	+2.16	+138.1	38	+12	+41.7	143.4	+1.03
1.046	5.61?	3.759	0.398	3.487	2.044	2.814	0.633	0.363	1.856	1.225
n	< 0.001	< 0.01	n	< 0.01	n	< 0.05	n	n	n	n

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Experimental and laboratory reports

Dextran exchange anemia and reduction in blood viscosity in the heart-lung preparation

With an observation upon the action of ouabain in anemic heart failure

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It has been demonstrated that the cardiac output is increased by intravenous infusion of 6 per cent dextran in amounts of 500 ml. in man[1] and in amounts of 80 ml. per kilogram in anesthetized dogs.[2] The mechanism of increase in cardiac output is not yet established. The rise in cardiac output was not dependent upon augmentation of blood volume, since cardiac performance was essentially unchanged when comparable expansion of blood volume was produced by infusion of whole blood.[3] *Further studies demonstrated that* the production of anemia by dextran exchange could increase cardiac output even though the blood volume had been reduced below normal and that increased filling pressure in the right heart was not essential for this response.[4] Thus it seemed that the hemodynamic effects of infusion of dextran must be related at least in part to the anemia produced thereby. The work of Justus and associates[5] suggested that dextran-induced anemia was associated with the release of a humoral substance which increased cardiac output. Other studies demonstrated that the adrenal glands were not essential for the change in cardiac output which followed dextran-induced anemia.[6] Gowdey[7] showed that the intravenous infusion of dichloroisoproterenol did not prevent the increased cardiac output of dextran-induced anemia in dogs. His study suggests that anemia does not increase cardiac output by the action of catecholamines or of sympathetic nerves upon the heart.

Insufficient attention has been given to *the possibility that the reduction in blood* viscosity associated with the infusion of dextran might be an important factor in the change in cardiac output. Accordingly, the decision was made to study the effects of dextran exchange anemia upon cardiac output, atrial pressures, and ventricular force in the heart-lung preparation, where neural, humoral, and vasodilator effects of anemia and tissue hypoxia would be minimized. In addition, blood viscosity was lowered without the production of anemia by the exchange of a Krebs solution–red cell mixture. In some preparations

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**[illegible] Associate Cardiac Laboratory, Department of [illegible] Medicine [illegible] of Medicine.

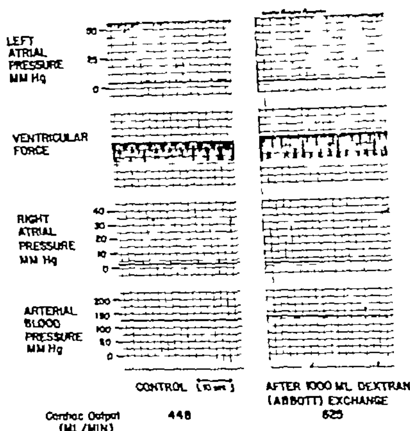


Fig. 1 Hemodynamic effect of 1 liter dextran exchange in dog heart lung preparation showing fall in atrial pressures and rise in ventricular force and blood pressure

dextran exchange was continued until there was anemic heart failure as judged by rising left atrial pressure and falling cardiac output and the action of ouabain was evaluated in these failing preparations

Experimental method

Dogs were anesthetized with intravenous sodium pentobarbital (22 mg per kilogram) Heart lung preparations were made from mongrel dogs of either sex as described previously [4] The Starling resistance was set at 85 mm Hg the blood entering the right atrium was kept at 37 to 39°C Direct measurements of cardiac output were made in duplicate by the collection of blood returning to the venous reservoir while a constant reservoir level was maintained with donor blood A strain gauge arch (120 ohms) was sutured to the surface of the left ventricle The placement and tension adjustments were as recommended by Cotten [5] and the tension was recorded by a Sanborn multichannel oscillograph In these experiments heart rates were determined from the strain gauge record Aortic pressure and atrial pressures were recorded by means of Statham transducers and a Sanborn four-channel direct writing oscillograph

In 9 preparations 1 liter of 6 per cent dextran in physiologic saline warmed to 38°C was exchanged for 1 liter of circulating blood To each bottle of dextran in saline was added sufficient $MgCl_2 \cdot 6H_2O$ $CaCl_2$ and KCl to give the following cation concentrations calcium 5 mEq per liter potassium 4 03 mEq per liter magnesium 1 33 mEq per liter After the administration of dextran changes in cardiac output ventricular force heart rate and atrial pressures were measured The maximum change in temperature after dextran was 0 9°C Samples of blood for determinatio

Table I. Hemodynamic effects of 1 liter of dextran exchange in heart-lung preparation

	Cardiac output (ml./min.)	Heart rate	Left atrial pressure (mm. Hg)	Left ventricular force (mm.)	Hematocrit	Viscosity centipoise
Control	405–625	126–165	3.8–8.8	5.5–15	48–58	3.0–5.0
Mean	(487)	(147)	(6.2)	(11.[illegible])	(53.1)	(3.97)
Maximum effect	566–1000	120–156	2.3–[illegible]4	8–23.5	7.5–17	[illegible]1–3.1
Mean	(666)	(135)	(4.6)	(15.5)	(13)	(2.66)
Net change from control	+66 to +375	0 to −12	−1.0 to −[illegible].4	+1.5 to +9.5		−0.5 to −2.00
Mean	(+180)	(−[illegible].4)	(−1.5)	(+4.[illegible])		(−1.31)
After 3[1] to 11[1] min.	545–750	108–150	1.3–8.7	7.5–18		
Mean	(600)	(1[illegible]9)	(5.4)	(1[illegible].9)		
Net change from control	+56 to +183	0 to −30	−[illegible].0 to +0.7	0 to +5.0		
Mean	(+113)	(−1[illegible].7)	(−0.[illegible])	(+1.7)		

[illegible]

Table II. Hemodynamic effects of Krebs-RBC suspension exchange in heart-lung preparation

	Exchange volume (ml.)	Cardiac output (ml./min.)	Heart rate	Left atrial press. (mm. Hg)	Left ventricular force (mm.)	Hematocrit	Viscosity centipoise
No. 152 Control	500	545	144	[illegible].7	13.5	48	3.7
After exchange		6[illegible]5	144	6.2	15.5	46.5	3.1
No. 153 Control	500	476	1[illegible]6	5.2	11.0	47.5	3.9
After exchange		526	114	5.3	11.0	46.0	3.3
No. 147 Control	1,000	417	16[illegible]	8.3	11.5	5[illegible]	4.3
After exchange		682	16[illegible]	7.1	16	38	2.3
No. 145 Control	1,000	500	140	5.3	17.5	40.5	3.5
After exchange		577	132	6.8	18.0	40.5	2.1

of hematocrit and viscosity were obtained during the control period and after dextran exchange. The viscosities were determined with the Ostwald viscosimeter at 37°C.

In 4 preparations the observations were similar except that blood viscosity was reduced without producing anemia. Dog red cells were separated from their plasma and the cells were resuspended in Krebs solution to reconstitute the original volume. Two animals received an exchange of 500 ml. of Krebs-red cell suspension, the other 2 received an exchange of 1,000 ml.

In 12 additional preparations the dextran exchange was carried out as before but was continued until heart failure occurred. Heart failure was considered to be present when left atrial pressure had risen

5 mm Hg or more and cardiac output was falling At this point the animals were given 250 µg of ouabain through the superior vena caval cannula The changes in cardiac output and pressures were observed for 6 minutes at this time an additional dose of 125 µg of ouabain was given In 9 animals an additional amount of 125 µg of ouabain was given after 2½ to 8¼ minutes In 3 of these experiments 0 5 Gm of glucose and 2 23 mEq of sodium bicarbonate were added to each 500 ml of dextran After the addition of sodium bicarbonate the dextran pH rose from 5 2 to 7 33

In 3 preparations heart failure was produced by serial exchanges of dextran as described above However the heart rate was held constant by stimulation of the right atrial appendage with a Grass stimulator thus driving the hearts at 192 198 and 204 beats per minute respectively Ouabain was administered as previously described

In 6 heart lung preparations ouabain was given as described but no dextran exchange was employed In 3 animals heart failure was produced by dextran exchange but ouabain was withheld The preparation was observed for 10 to 12 minutes after heart failure occurred then an exchange with 1 000 and 1 500 ml of whole blood was performed in order to determine whether the heart failure could be reversed by correcting the anemia

Results

Hemodynamic effects of dextran exchange The exchange of 1 liter of dextran for blood in the heart lung preparation required approximately 2 minutes and was followed by rather consistent results Cardiac out

Table III Hemodynamic effects of ouabain in anemic heart failure

	Cardiac output (ml /min)	Heart rate	Left atrial pressure (mm Hg)	Ventricular f c (mm)†	Hematocrit‡
Control	395 – 612 (434)	138 – 168 (157)	3 8 – 9 7 (7 3)	7 0 – 16 5 (11 9)	39 5 – 56 5 (47 6)
After 1 liter of dextran	438 – 750 (549)	132 – 167 (143)	2 6 – 13 0 (6 6)	8 5 – 25 5 (14 3)	6 – 10 0§ (8 4)
Heart failure	341 – 566 (438)	96 – 167 (124)	8 5 – 17 8 (12 6)	5 5 – 19 0 (10 4)	2 – 7 (7)
After ouabain	417 – 732 (516)	90 – 162 (118)	2 8 – 16 8 (8 3)	9 – 42 (17 0)	

[illegible]
[illegible]
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[illegible]

Table IV Hemodynamic effects of ouabain in normal heart lung preparation

	Cardiac output (ml / min)	Heart rate	Left atrial pressure (mm H)	Ventricular force (mm)
Control	403 – 465 (438)	144 – 156 (149)	1 9 – 7 8 (4 9)	10 5 – 1 5 (13)
After ouabain	441 – 494 (467)	157 – 150 (143)	1 0 – 5 2 (2)	11 – 26 (16 3)

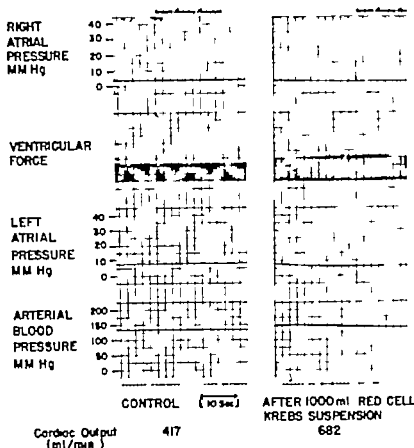


Fig. 2. Hemodynamic effect of exchange of 1 liter of Krebs red cell suspension in the dog heart-lung preparation showing a decrease in atrial pressures and an increase in ventricular force and blood pressure.

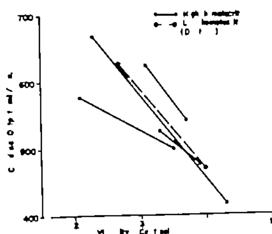


Fig. 3. Graph of relation between reduction in blood viscosity and increase in cardiac output. The broken line represents the average of 8 experiments with a 1 liter dextran exchange. The solid lines show 4 individual experiments with a 1 liter exchange of Krebs red cell suspension.

put and ventricular force began to increase during the dextran exchange and reached peak values within 1 or 2 minutes after its completion. An example of the hemodynamic changes is shown in Fig. 1. Table I summarizes the results obtained in 9 animals. The cardiac output increased in each study with the average increment equal to 37 per cent above control. Left atrial pressure declined in each instance with a mean decrease of 1.5 mm Hg. Changes in right atrial pressure were similar but of smaller magnitude. Ventricular force increased an average of 38 per cent and viscosity decreased an average of 33 per cent. When the observations were repeated 3½ to 11½ minutes after the exchange the changes were still present but were of lesser degree.

Krebs red cell suspension exchange. This procedure was carried out in 4 prepara-

tions and the results are shown in Fig. 2 and in Table II. The exchange of 500 ml produced in 2 animals a lesser decrease in viscosity and a lesser elevation of cardiac output than those in the dextran-exchange experiments, with little change in left atrial pressure and left ventricular force. A 1 liter exchange in 2 animals was followed by a greater decrease in viscosity and in one more striking hemodynamic changes (Figs. 2 and 3). The graph in Fig. 3 shows the slope of the lines relating increase in cardiac output to decrease in blood viscosity. In 2 of the 4 Krebs red cell exchange experiments the slope was similar to that of the average of the dextran exchange experiments. In the other 2 there was a somewhat smaller increase in cardiac output in proportion to reduction in viscosity.

Anemic heart failure. The results of 12 experiments are summarized in Table III. In these heart-lung preparations there was an initial dextran exchange of 1 liter with hemodynamic results similar to those described in the first paragraph of the section on *Results*. In 3 of these 12 animals the heart rates were held constant by electrical stimulation of the right atrium; the results in these 3 preparations were

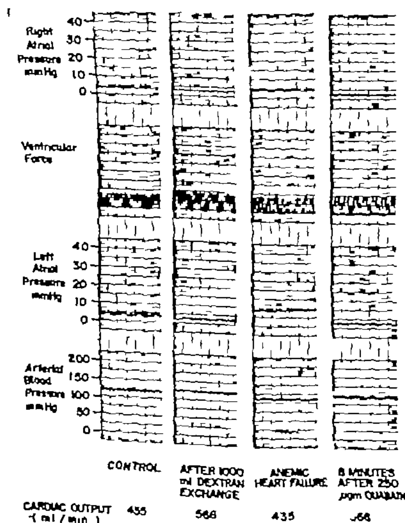


Fig. 4. Effect of ouabain in anemic heart failure. After ouabain, left atrial pressure fell from 9 to 3 mm Hg and cardiac output increased from 435 to 566 ml per minute. Blood pressure fell during heart failure and increased after ouabain.

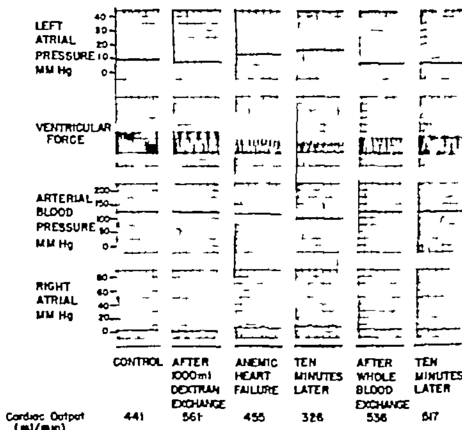


Fig. 5. Production of anemic heart failure by continued dextran exchange. After 1 liter dextran exchange there was an increase in cardiac output and a decrease in atrial pressures (*second column from left*). With anemic heart failure left atrial pressure rose 5 mm Hg (*third column*) and blood pressure fell. After 10 minutes there was a further rise in atrial pressure (*fourth column*). After the hematocrit was restored to normal, left atrial pressure fell from 16 to 6 mm Hg and ventricular force, blood pressure, and cardiac output increased (*fifth and sixth columns*).

similar to those to be described below, and except for heart rates they are included in the averaged data of the other 9. After the 1 liter dextran exchange additional exchanges of 200 to 300 ml were carried out at intervals of 2 to 3 minutes until left atrial pressure had risen 5 mm Hg above control; anemic heart failure was then considered to be present. At this point the total amount of dextran exchanged was 1,500 to 4,000 ml. The cardiac outputs were only slightly lower than control (Table III) but were well below the peak values after dextran exchange (Fig. 4). The hematocrits were from 2 to 7 per cent at the onset of heart failure. The administration of ouabain was followed by a striking decrease in left and right atrial pressures in each animal except one. The mean decrease in left atrial pressure was 4.3 mm Hg. In 6 instances left atrial pressure returned to control values (Fig. 4). Cardiac output increased after ouabain in each instance and the average after ouabain was higher than in the controls. Ventricular force also increased after ouabain in each study. The pH of dextran with added electrolytes used in these studies was 5.2. In order to be certain that the changes observed did not reflect pH alterations, in 3 of the foregoing experiments the dextran pH was adjusted to 7.33 at 37°C by the addition of 2.23 mEq. of sodium bicarbonate and 500 mg. of dextrose to each 500 ml. bottle. The initial increase in cardiac output and decrease in left atrial pressure were similar to those observed in the earlier studies with dextran

exchange Furthermore anemic heart failure occurred at a similar hematocrit value and the response to ouabain was comparable to that in the other experiments

Ouabain in the normal heart lung preparation In each animal ouabain 375 to 500 μg lowered atrial pressures and increased cardiac output and left ventricular force (Table IV) The changes were in the same direction as those observed in the failing preparations but were of lesser magnitude

Reversibility of anemic heart failure That the response of anemic heart failure to ouabain was not related to spontaneous recovery was shown by control studies in 3 heart lung preparations In these animals anemic heart failure was induced as described previously The preparations were then observed with repeated measurements of pressures and cardiac output for 10 11 and 12 minutes respectively There was no improvement in cardiac function in fact cardiac output fell and atrial pressures remained unchanged or rose (Fig 5) The animals were then given an exchange of the first 1 000 to 1 500 ml of whole blood removed during the dextran exchange raising the hematocrits from 8 6 and 3 per cent to 38 42 and 42 per cent respectively After this exchange the cardiac outputs rose and atrial pressures fell (Fig 5) Ventricular force rose in 2 of the 3 animals

Discussion

The physical relationship between changes in hematocrit and alterations in circulating blood viscosity is not a simple one It is well established that the graphic relation between changes in hematocrit and in vitro viscosity follows a curved line rather than a straight one[19] It has been shown that one cannot predict the hemodynamic effects of changing viscosity by simple substitution in the denominator of the Poiseuille equation Effective blood viscosity is markedly altered by shear rate[21] and by the size of the tube through which the blood passes[18] For example Gregersen and associates[21] using a Polaroid viscometer showed that at a constant high hematocrit viscosity could be increased forty fold merely by decreasing shear rate from 20 sec ¹ to 0 2 sec ¹ Fahreus and Lindqvist[1] demonstrated a decrease in the apparent viscosity of blood flowing through tubes below 300 micra in diameter at a pressure of 100 mm Hg However they were unable to force the blood through tubes of capillary size

Thus it becomes difficult to predict the effect of alteration in blood viscosity as measured in vitro upon the circulation of the intact animal The Fahreus Lindqvist effect may not be applicable to tubes which are the size of capillaries through which presumably most of the blood passes Furthermore the exact shear rates in the different areas of the circulation are unknown Thus the precise hemodynamic effects of alterations in blood viscosity must be determined in the intact animal The effects of reduction and increase in blood viscosity upon hemodynamics have been studied in limited areas of the circulation For example *Mendlowitz*[13] by studying the human digital circulation found effective blood viscosity to be 80 per cent of normal when the hematocrit was lowered to 17 per cent The hemodynamics of alterations in blood viscosity have been studied in the perfused dog's hind limb by Pappenheimer and Maes[14] and by Levy and Share[15] The latter authors found that the apparent viscosity of anemic blood was only slightly greater than that of plasma until the hematocrit was raised to about 30 per cent The viscosity in vivo was much lower than that measured in vitro with a high velocity viscometer The influence of pressure upon apparent viscosity depended upon the degree of vascular dilation In the denervated hind limb viscosity was independent of pressure but became dependent upon pressure in the maximally dilated circulation

Our studies demonstrate a consistent increase in cardiac output after the production of dextran exchange anemia in the heart lung preparation It seems likely that the results are related to a reduction in viscosity In the heart lung preparation Gremels and Starling[16] found that progressive hypoxemia did not affect cardiac output until oxygen saturation fell to 40 per cent Below this saturation the heart dilated and cardiac output fell Thus myocardial hypoxia alone would be ex

pected not to change or to decrease cardiac output and ventricular force. The possibilities of a neural or humoral effect seem minimal. Furthermore, similar increases in cardiac output and ventricular force were observed when viscosity was decreased without the production of anemia. The results were not related to an increase in temperature, to a lack of glucose, to the acidity of the dextran, nor to a rise in atrial pressures. Despite the complexities of the relation between the change of in vitro viscosity and the blood flow in vivo, the increases in cardiac output observed in these studies were remarkably comparable to the measured reduction in viscosity. Unfortunately, one cannot use these data to predict the apparent viscosity effects of anemia in the intact animal. The degree of anemia produced in these experiments was quite severe, although similar degrees are occasionally found in man. The dextran used in these studies, being more viscous than plasma, reduced blood viscosity less for a given degree of anemia than one finds in patients. Since the systemic arteries and capillaries, except for the coronary circulation, are excluded in the heart-lung preparation, one might well find a different change in apparent viscosity in the intact animal. Furthermore, the pulmonary blood flow in these experiments was one third or less of what one might expect in the resting intact animal.

Despite these limitations it would appear that a reduction in blood viscosity may be an important factor in the increased cardiac output of anemia. It is clearly not the only factor. Justus and co-workers[4] have demonstrated a humoral factor in dextran-induced anemia. Crawford and associates[17] have demonstrated that perfusion of the dog's hind limb with venous blood can cause vasodilatation without a reduction in blood viscosity. The magnitude of the increased cardiac output which may be found in human subjects with anemia, at times exceeding the normal resting value by more than 100 per cent,[18] seems to be greater than could be explained by a reduction in viscosity. Nevertheless, it should be recalled that atrial pressure fell as cardiac output rose during our dextran exchange studies. If atrial pressures had been returned to normal by raising the venous reservoir, the increase in cardiac output would undoubtedly have exceeded that which was observed.

Our experiments show that it is possible to produce experimental anemic heart failure in the heart-lung preparation by lowering the hematocrit to 2 to 7 per cent. It seems quite clear that cardiac performance can be improved by digitalis glycosides under these circumstances. This demonstration is of some clinical interest, since Lahiri[19] found little or no decrease in ventricular diastolic pressure after digoxin in human circulatory congestion associated with beriberi or anemia. Anemic heart failure in man is often associated with pre-existing heart disease; thus the argument for digitalis seems to be even more compelling. The reversibility of anemic heart failure by restoration of the hematocrit to normal makes this a useful preparation for the study of experimental heart failure.

Summary

In dog heart-lung preparations, a 1 liter dextran exchange lowered hematocrits from an average of 53 to 13, with an average increase in cardiac output of 38 per cent and an in vitro decrease in blood viscosity of 33 per cent. Atrial pressures fell and ventricular force rose. When blood viscosity was reduced without anemia by an exchange of dog red cells suspended in Krebs solution, there was a similar change in cardiac dynamics. These results suggest that reduced blood viscosity is an important factor in the increased cardiac output of anemia. When hematocrits were lowered to 2 to 7 per cent by further dextran exchange, anemic heart failure resulted with rising atrial pressures and declining cardiac output. After 375 to 500 µg of ouabain, atrial pressures fell and cardiac output rose in 11 of 12 preparations with anemic heart failure. The anemic heart failure could also be improved or eliminated by restoration of the hematocrit to normal.

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Hemodynamic effects of bradykinin and gastrin in the stomach

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There is suggestive evidence that gastric secretion may be dependent upon physiologic changes in the flow of blood to the stomach. The mechanical reduction of blood flow in the perfused histamine-stimulated[1] or resting[2] stomach results in a corresponding decrease in the rate of secretion by the stomach. A number of studies employing a variety of acute physiologic or morphologic techniques have reported that the flow of blood to the entire stomach or to the gastric mucosa is increased by histamine,[3,4] vagal activity,[5] acetylcholine,[4] and other gastric secretory stimulants.[6] Conversely, a diminished gastric blood flow has been reported in response to a number of gastric secretory inhibitors: sympathetic stimulation, vagotomy, and vasopressin,[5] norepinephrine,[5,6] and epinephrine.[5,6] There are reports, however, which contradict some of these findings.[7,9]

The hemodynamic effects of gastrin in the stomach are not known. Similarly, the vasoactive properties of bradykinin have not been studied in the stomach, nor are the gastric secretory responses to this agent known. Bradykinin or a similar polypeptide is involved in the function of other gastrointestinal glands[10,11] and is a potent vasodilator in all circulatory systems studied to date.[11]

If an alteration of blood flow to the gastric mucosa is a physiologic determinant of gastric secretion, one would anticipate that gastrin would be a vasodilator in the stomach and that bradykinin would accelerate the gastric secretory rate if it also dilated the gastric circulation. These hypotheses were tested in acute experiments employing a constant flow perfusion of the canine stomach.

Methods

Acute experiments were performed on 21 dogs which weighed 10 to 20 kilograms each. Sixteen of these animals were anesthetized with pentobarbital sodium (30 mg. per kilogram) and a finger pump was used to perfuse the stomach at a constant flow (30 ± 5 ml. per minute) through the left gastric and left gastroepiploic arteries by a previously described technique.[1] This flow results in a perfusion pressure which is comparable to systemic arterial pressure. An equilibration period of 30 minutes was allowed for stabilization, during which time carotid arterial, portal venous, and gastric perfusion pressures were monitored continuously. In half the dogs graded doses of histamine (ranging from approximately 0.1 to 50 μg per minute) were infused directly into the perfusion circuit for 30 minutes according to the

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Received for publication Oct. 28, 1963.
*[illegible] Walter Reed Army I[illegible] of Resea[illegible] R[illegible] Army Med[illegible] Washington, D.C. [illegible]

following schedule the lowest dose was infused initially and pressure in the perfusion circuit was observed until it had stabilized (usually less than 1 minute) after which the next higher amount of histamine was infused Ten minutes were required to complete this succession of progressively larger doses of histamine at the end of this time a fixed near maximal dose (25 μg per minute) was infused over the subsequent 20 minutes Another 30 minute period of equilibration was then allowed after which an infusion of gastrin was started following the schedule outlined above for histamine Pressures were recorded continuously during the periods of infusion of the drugs In the other 8 dogs a similar comparison of gastric vascular responses was made between histamine and bradykinin † Again each agent was administered directly into the perfusion circuit in graded doses over a period of 30 minutes according to the schedule outlined previously The order of infusion of histamine and bradykinin (8 dogs) or histamine and gastrin (8 dogs) was randomized

The amount of drug administered per minute was divided by the flow of blood to the stomach of the individual dog and expressed as a drug concentration in the blood perfusing the stomach For gastrin this concentration range was 0 5 to 60 μg per milliliter of blood For bradykinin and histamine the range was 0 001 to 1 0 μg per milliliter of blood The constant dose infused for each agent during the final 20 minutes of each experimental period was approximately 500 μg per minute for gastrin and 25 μg per minute for bradykinin or histamine

Pressures in the perfusion circuit in a branch of the portal venous system near the stomach and in a common carotid artery were monitored with a strain gauge transducer connected to a recorder Local vascular responses to these agents were expressed in terms of peripheral resistance units (P R U) obtained from the quotient of the mean pressure gradient across the stomach (arterial minus venous pressures in millimeters of mercury) and the constant pump flow (in milliliters per minute) measured directly from a graduated reservoir in the pump circuit

Since the secretory response of the stomach to bradykinin has not been described 5 additional animals were studied in the following way Each dog was anesthetized with morphine (16 mg subcutaneously) and chloralose (75 mg per kilogram intravenously) in order to provide a tonic vagal effect and allow more sensitive responses to the action of bradykinin and histamine After ligation of the pyloric end of the stomach the celiac axis was exposed and a polyethylene cannula was threaded into the celiac artery via the ligated hepatic artery Gastric juice was collected by means of a glass cannula inserted through the stomach wall during 30 minute periods of control histamine stimulation (10 μg per minute) and bradykinin stimulation (10 μg per minute) Infusions of drugs and control periods were randomized from dog to dog Drugs were infused into the celiac artery with a pump Gastric collections from each 30 minute period were analyzed for volume pH free and total acid (by titration against 0 05 N sodium hydroxide with bromphenol blue to a pH of 3 5 and phenol red to a pH of 7 0) and pepsin *

Results

Hemodynamic effects Histamine dilated the gastric circulation equally in both groups of 8 dogs (Figs 1 and 2) The critical concentration beyond which resistance to blood flow across the stomach began to decline appreciably was 0 1 μg of histamine base per milliliter of blood perfusing the stomach These results correspond to what has been reported for histamine with this experimental technique

Similarly gastrin was a vasodilator of the gastric vascular bed (Fig 1) Resistance

Th [illegible] employed [illegible] was kindly supplied by Dr [illegible] I G [illegible] Th [illegible] virtually free of h[illegible] [illegible] per [illegible] that 20 mg [illegible] [illegible] [illegible] Heidenhain pouch [illegible] highly [illegible] by 1 mg of h[illegible] [illegible]
†Kindly supplied by [illegible] Pharmaceutical [illegible] N J [illegible] Th[illegible] acid med[illegible] (pH = 4 0) In the amount [illegible] there was [illegible] effect [illegible] the pH of th[illegible] blood

*Th[illegible] method [illegible] pepsin was based on th[illegible] reported by [illegible] and [illegible] modified by D[illegible] G [illegible] Dr J W M[illegible] and M[illegible] J J [illegible] ([illegible])

Table I. Comparison of gastric secretory responses during 30 minute control periods and during 30 minute infusions of histamine and bradykinin in 5 dogs

Dog number	Sample	Volume (ml.)	pH	Free acid (mEq./L.)	Total acid (mEq./L.)	Pepsin (per cent activity)
1	Control	6	1.30	0.5	49.2	1.56
	Histamine	9	1.40	70.5	77.0	1.24
	Bradykinin	10	2.10	13.2	39.6	2.70
2	Control	6	1.50	61.7	0.5	0.59
	Histamine	25	1.40	9.2	97.5	0.19
	Bradykinin	6	1.30	81.5	97.5	0.27
3	Control	8	1.95		48.4	0.71
	Histamine	16	1.55			0.49
	Bradykinin	14	3.00			0.23
4	Control	0		0.0	0.0	0.00
	Histamine	3	1.00	11.0	22.0	6.77
	Bradykinin	8	2.45	4.4	27.5	3.11
5	Control	3	1.80			3.69
	Histamine	15	1.30	81.4	88.0	1.83
	Bradykinin	6	2.00		19.8	2.97
	25 μg of pepsin					10.64

to blood flow fell appreciably when concentrations of gastrin in the perfusate exceeded 10 μg per milliliter of blood. Gastrin appears to be about 1/100 as potent a vasodilator as histamine in the perfused stomach.

Bradykinin was also a vasodilator in the stomach (Fig. 2). As with histamine, the fall in resistance became apparent at blood concentrations exceeding 0.1 μg per milliliter. On a weight basis, bradykinin and histamine appear to be equipotent dilating agents in this preparation.

Gastric vascular resistance was decreased by the progressive increase in doses of each of the three agents employed over a period of 10 minutes. For the next 20 minutes a constant near maximal dose of each substance was infused and resistance to blood flow was calculated. Both bradykinin and gastrin were able to maintain a dilated gastric circulation for 20 minutes, whereas resistance had returned to preinfusion values at the end of 30 minutes of continuous infusion of histamine (Fig. 3).

Systemic arterial and portal venous responses to these agents were small, probably due in large part to the injection site, which allowed both the stomach and liver to clear these materials. Maximal declines in systemic arterial pressure with histamine, gastrin, and bradykinin averaged −8, −7, and −5 mm. Hg, respectively. Maximal changes in portal pressure in response to the same three agents averaged +1, 0, and −1 mm. Hg, respectively.

Secretory effects. The gastric secretory response to bradykinin and histamine was studied in 5 additional dogs under more physiologic conditions (Table I). Bradykinin stimulated gastric secretory volumes which were comparable to those induced by histamine. The pH values were higher in 4 dogs with bradykinin than with histamine, and were higher than control values in 3 dogs. There seemed to be no consistent differences in acid and pepsin secretion between histamine-stimulated and bradykinin-stimulated stomachs.

Discussion

Since there appears to be some correlation between the secretory and the vasodilating properties of several common gastric stimulants,[3,4] it seemed reasonable to expect that gastrin would dilate the circulation of the stomach and that bradykinin would stimulate gastric secretion if it also dilated the gastric circulation. These expectations were fulfilled only in part and require considerable qualification.

This investigation has demonstrated that gastrin will dilate the gastric circula-

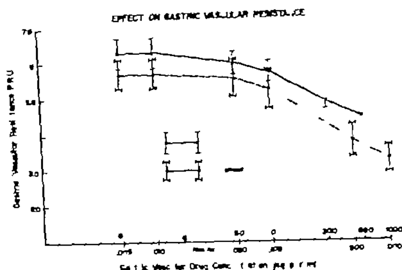


Fig 1 Comparison of the effects of gastrin and histamine on resistance to blood flow across the perfused stomach of 8 dogs One standard error of the mean is plotted above and below each value

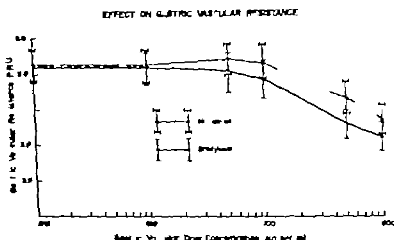


Fig 2 Comparison of the effects of bradykinin and histamine on resistance to blood flow across the perfused canine stomach One standard error of the mean is plotted above and below each value

tion and that bradykinin will initiate gastric secretion when very large amounts of these agents are employed The concentrations of gastrin or histamine in the perfusate which effected dilation in this preparation are many times greater than the concentrations which are normally needed to induce a maximal gastric secretory rate [11,12] Thus a continuous intravenous infusion of histamine of approximately 2 μg per kilogram per minute induces a maximal gastric secretory response in the intact unanesthetized dog [4] This would correspond to a concentration of about 0 2 μg per milliliter of blood assuming rapid distribution which is one fifth of the blood concentration of histamine in the perfusate of this preparation at which dilation began to occur (Figs 1 and 2) The same considerations would apply to the gastrin (which is approximately 1/20 as potent a secretory stimulant and 1/100 as potent a dilator in this preparation) Thus the amounts of histamine

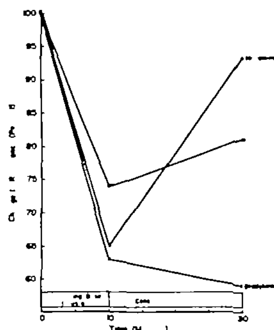


Fig. 3. Comparison of the duration of depressor effects of gastrin, bradykinin and histamine on gastric vascular resistance.

which were required to induce a significant increase in the output of gastric juice imply considerable secretory insensitivity of the perfused stomach in this preparation. In addition, the nature of the juice secreted in response to bradykinin (Table I) suggests that this might represent some degree of injury and transudation rather than a primary effect on parietal cell secretion. Finally, the failure of histamine to maintain a dilated bed in the perfused stomach preparation for as short a while as 30 minutes (Fig. 3) scarcely lends support to the idea that the secretory effects of histamine depend upon its ability to dilate the gastric circulation. It is well known that histamine can induce and maintain a hypersecretory state in the unanesthetized canine stomach for hours.

The most likely reasons for the apparent vascular and secretory insensitivity of the stomach observed in these investigations are technical. Anesthesia, especially pentobarbital, depresses gastric secretory activity,[16] and the pump-perfused stomach has been found to respond sluggishly to stimulants.[1,2] In addition, it is possible that the slow infusion of drugs into the arterial circuit did not allow adequate mixing and a uniform distribution to all parts of the stomach. Until a technique is available for continuous measurement of gastric blood flow in the unanesthetized animal, the question of an artifically insensitive circulation will remain problematical.

The chemical structure of gastrin has not been determined, although the hormone is believed to contain one or more polypeptide moieties.[14] It seems unlikely, however, that gastrin is in part bradykinin, since it exerts no effects on the smooth muscle of the guinea pig ileum or on the blood pressure of the cat, both of which respond dramatically to small amounts of bradykinin.[11,18]

Summary

A comparison was made between the effects of bradykinin, gastrin, and histamine on vascular resistance in the perfused canine stomach. All three substances were found to dilate the gastric circulation. Bradykinin was observed to stimulate the gastric secretory volume. The amounts of histamine and gastrin required to achieve the dilator effects in this preparation, however, were considerably greater than the amounts of these substances which maximally stimulate gastric secretion in the intact, unanesthetized animal.

I am indebted to F. Lyle Brown, Donald I. Collin and Miguel R. Ramirez for technical assistance, to Dr. Gerard Smith for the gastric analyses, and to Dr. David F. Bass and Dr. Robert L. Vick for advice.

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Comparative efficiency of stethoscopes

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Nearly a century and a half has elapsed since Laennec introduced the stethoscope—originally, it is recorded, a quire of paper rolled into a cylinder for purposes of modesty in listening to the heart of a young lady. Today this crude acoustical instrument remains the most expedient means of conducting sound from the chest wall to the ear. It is the most used instrument in the physician's bag, and has indeed become a veritable symbol of medicine. Perhaps one should approach with some reverence any appraisal of the efficiency of this device on which so much of our clinical knowledge of heart disease has been built. But there is, after all, no magic to its hollow tubes: the magic is in the unparalleled sensitivity and versatility of the human ear (and of course in that most important link in the chain, that perceptual link between the two earpieces). In an age of increasingly complex medical gadgetry we might profitably re-examine some of the physical properties of this simple unstandardized tool to determine, in short, what constitutes an efficient stethoscope.

The auscultatory sounds

Cardiovascular sounds are lower both in frequency and in intensity than those to which the ear is ordinarily attuned. The vast proportion of vibrational energy produced by the heart lies below the frequency range of human hearing and is often more readily appreciated by palpation; only a small fraction is heard stethoscopically, and its intensity normally decreases rapidly above 40 to 50 cycles per second (c.p.s.) to exceedingly small signals in the range of middle C on the piano (256 c.p.s.). Were it not for the fact that there is an almost reciprocal increase in the sensitivity of the ear with increasing frequency, we would hear little but low rumbling sounds from the precordium.

The frequency range of cardiac auscultation lies mainly between 50 and 500 c.p.s., although sounds an octave or two higher doubtless do contribute because of the ear's nearly maximum sensitivity in that range. When one considers that human hearing extends on up to 10 to 15 thousand cycles per second, the pitch of most cardiovascular sounds is seen to be at the bottom of the scale in the region of relatively poor hearing acuity. Therefore, if we are to detect the fainter, less obvious murmurs of early valvular heart disease, the ear must work very close to threshold levels, and any measures which improve stethoscopic audibility can contribute materially to auscultatory performance. One cannot alter appreciably the intensity and frequency of the sounds at the chest wall except by means of a few clinical maneuvers (such as exercising the patient, turning him on his left side, or having him suspend respiration). Nor can one improve his own hearing acuity (unless perhaps by electronic augmentation). One can

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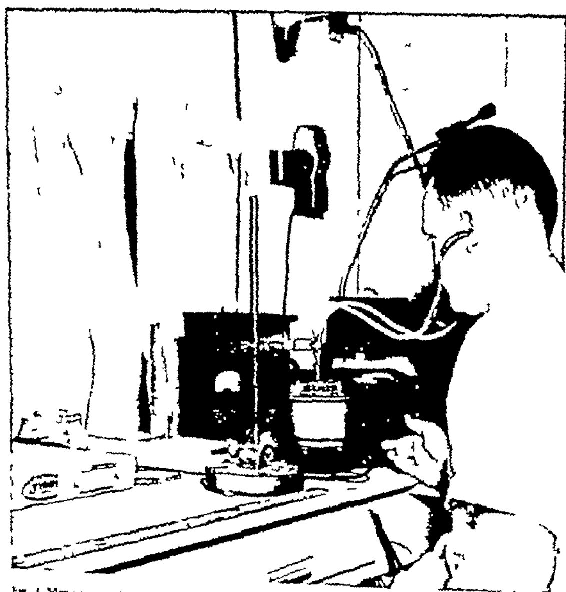


Fig. 1 Measuring stethoscope efficiency. In this experiment, tape recorded sounds are reproduced in an artificial precordium, a fluid filled medium which simulates the acoustical impedance of the chest. This is held against the stethoscope chestpiece at a uniform pressure. The observer turns up a calibrated volume control until the sounds become audible, thereby measuring the threshold of stethoscopic audibility.

however, use a stethoscope of good efficiency. And he can further enhance audibility by reducing the level of ambient noise in the examining room.

Stethoscope characteristics

It is possible to measure the efficiency of a stethoscope in much the same way that an audiogram is determined. Fig. 1 illustrates a practical method which, although not quite so objective as measuring the transmission of sound with microphones, does evaluate the instrument in terms of the end result, that of actual performance on the precordium. Either pure tones of various frequencies or tape recorded heart sounds and murmurs may be used for the threshold determinations. It is the threshold level which must be measured rather than the intensity level of the sound because the ear is a notoriously poor comparator of intensities.

Utilization of this technique with averages of repeated trials makes it possible

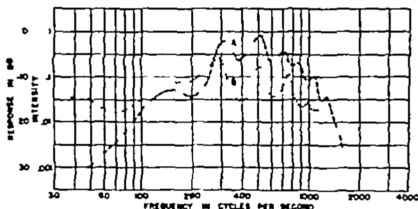


Fig. 2. Response characteristics of stethoscopes to various frequencies. *A*, Diaphragm type stethoscope. *B*, Bell type stethoscope. From Olson.

to obtain stethoscope response curves similar to those plotted from electronic measurements of the transmission of sounds (Fig. 2). The inequality of responsiveness at different frequencies, which gives the alternate peaks and valleys in the curves, is characteristic of acoustic stethoscopes and is due to resonances in the air columns. Certainly, such curves bear little resemblance to the linear response curve of a high fidelity instrument. But the fact remains that for clinical purposes it is more important to detect a murmur than to hear it with high fidelity, at least at the present state of our knowledge; distortion of the sounds is a secondary consideration. Preferential transmission in the low frequency range is provided by the bell chest piece (curve *B* in Fig. 2) which is used in listening to, for example, the presystolic rumble of mitral stenosis or the bass thud of the third or fourth heart sounds. Conversely, unless one listens also with the diaphragm chestpiece, higher pitched sound, such as the diastolic murmur of early aortic insufficiency or the Graham Steell murmur, may be readily missed.

Common practice is to select a stethoscope which is comfortable, convenient to carry, and looks well and "sounds right." Repairs which are made to it through the years may be given little thought or may even be left more or less to improvisation. Generally, we tend to become accustomed to the characteristics of this personalized tool and oblivious of its failings. But just how much various stethoscopes can differ in efficiency is demonstrated in the following experiment from which Table I is derived.

Thirty-three stethoscopes were borrowed at random from the examining room of a large general hospital and from members of its staff. They were compared by a single observer with a conventional stethoscope of good design according to the method illustrated in Fig. 1. Threshold measurements were made for both the heart sounds and the diastolic murmur recorded on magnetic tape from a patient with aortic insufficiency. The tests were made in a soundproof room under conditions of no audible ambient noise and were then repeated with reproduction in the room of a 65-decibel level of "white noise" (i.e., noise composed of more or less equal intensities of all frequencies of the audible spectrum).* Only the bell chestpieces were used in this comparison in order to avoid the variable of diaphragm characteristics. The results are set forth in Table I in terms of the relative level of intensity in decibels required for audibility of the heart sounds and the murmur, both with and without the background noise.

As might be anticipated, the most noticeable differences in efficiency of the stethoscopes were found under the conditions of environmental noise in which three fourths of the 33 instruments were down 7 decibels or more below acceptable standards of efficiency, which means that a murmur would have to be five times the intensity to be perceptible with that stethoscope as with one of reasonably good efficiency (the decibel scale being a logarithmic one). Some 7 of the 33 were down as much as 12 decibels, which represents a

*Although 65 db. of white noise may not be truly representative of the [illegible] level of background noise encountered in hospital wards (because [illegible] contains [illegible] high frequencies which may have a greater masking effect), the [illegible] here was primarily that of comparing different stethoscopes at [illegible] level of noise.

factor of 15 1 Similar results were obtained for audibility of both the heart sounds and the murmur only 1 or 2 of the stethoscopes checking out as well as the standard model in over all efficiency On the basis of these findings about one third of the stethoscopes tested could be considered to be adequate for cardiac examination Nearly all of them could be improved and were After correction of some of the worst of the common faults cited below the 33 stethoscopes were again checked in the same manner and the threshold readings were then compared with the previous ones The resultant improvement ranged up to 15 decibels or more with an average under the ambient noise conditions of 5 5 decibels Such an increase in efficiency (5 5 db = 7 1) is immediately noticeable clinically Admittedly hospital stethoscopes are frequently less carefully selected and cared for than those which belong to individuals Nevertheless their pathology is more or less common to all

Leaks By far the greatest impairments in efficiency observed were those due to leaks—at the earpieces the flexible tubing the changeover valve or the chestpiece

A well-enclosed acoustic pathway is essential for the transmission of sounds from the chest wall to the ear and the introduction of even a small leak causes a precipitous drop in the efficiency of transmission Losses of as much as 10 to 15 decibels from leaks alone are not unusual (e g stethoscope No 7 had a chipped bell No 19 had a crack in the flexible tubing No 32 had cracked earpieces) Moreover such leaks admit ambient noise into the system so that their deleterious effect becomes greater at the higher levels of environmental noise A familiar clinical illustration of this is the difficulty in hearing sounds from a very hairy chest unless one achieves an adequate acoustic seal by application of water or K Y jelly to the hair

Leaks in the changeover valve of the chestpiece are readily demonstrable by blowing into the tubing with the opposite orifice occluded and those around cracked or ill fitting earpieces can be estimated by observing the amount of background noise which is audible with the earpieces in place but with the tubing or chestpiece occluded Probably the best simple test of the integrity of the acoustical seal of the over all system is *withdrawal of the chestpiece quickly from the precordium which should produce a change in pressure painful to the ear*

Tubing The total enclosed volume of the stethoscope bears a direct relationship to its efficiency of transmission According

*Table I Comparison of efficiency of 33 stethoscopes**

Stethoscope number	*Room quiet (0 db)*		*Ambient noise (65 db)*	
	Heart sounds	*Murmur*	*Heart sounds*	*Murmur*
1	52	30	31	15
2	52	38	28	16
3	52	38	27	16
4	53	36	27	15
5	52	31	29	19
6	52	30	27	19
7	41	29	7	0
8	57	38	17	12
9	57	32	20	6
10	51	30	1	7
11	54	37	33	18
12	51	35	23	11
13	54	34	20	10
14	50	31	28	7
15	50	32	33	19
16	51	30	20	3
17	60	46	1	14
18	52	32	30	11
19	54	38	22	12
20	55	45	28	20
21	51	36	26	11
22	54	45	33	20
23	52	36	25	17
24	52	39	28	17
25	53	36	33	18
26	51	30	28	8
27	51	37	26	7
28	51	33	31	10
29	52	37	16	11
30	52	38	16	10
31	49	32	31	14
32	57	40	26	17
33	50	37	25	15
Standard stethoscope	57	38	32	22
Average db	52	33	27	10

*Expressed [illegible] terms of decibel [illegible] This [illegible] the higher the number of decibels the lower the intensity of sound required [illegible] audibility [illegible] the greater the efficiency of transmission

to Rappaport and Sprague[8] the amplitude of variations in pressure which reaches the ear is inversely proportional to the internal volume of the system. It would then follow that tubing of almost infinitely small internal diameter would be the most desirable throughout were it not for the fact the sound is a longitudinal wave motion involving movement of air in the columns and frictional resistance to this movement imposes yet another limitation.[8] With internal diameters less than one eighth of an inch frictional losses become excessive especially at the higher frequencies. Diameters of one eighth to three sixteenths of an inch are thus compromises between considerations of volume and friction. Unless its inside surface is smooth and its length quite short, tubing of one eighth inch or less will attenuate appreciably the higher frequencies, those which often characterize faint murmurs and are at best of extremely low amplitude near the threshold of audibility.

Certain physical properties of the flexible tubing bear on efficiency. It should be of a relatively unyielding rather than an elastic consistency, for any "give" of the walls subtracts from the amplitude of the pressure waves within. The worst type of tubing is the commonly used soft gum rubber, which is often thin walled and has a rough interior surface that further increases frictional losses. Noticeably better results can be obtained with some of the newer *plastic tubings such as* Tygon, the consistency of which affords a damping quality which also provides superior rejection of ambient noise.

Logically, the longer the transmission pathway the greater the losses, all other factors remaining equal.† The very short lengths employed in stethoscopes used for auscultation of fetal heart sounds (and in the old monaural instruments still seen on the wards in Europe) are not acceptable to most physicians for auscultation of the chest. A practical compromise length is *20 inches over all from chestpiece to earpiece*—several inches shorter than many stethoscopes in use. Of the 33 stethoscopes in the above mentioned experiment, half were 26 inches or more over all, several as much as 28 inches.

Apparently at one stage in the evolution of the stethoscope it was postulated that two tubes would transmit sound from the chestpiece to the binaural twice as well as one, so that it has become accepted practice to incorporate two separate flexible tubes the entire distance between the chestpiece and the binaural. Not only does that design add unnecessarily to the total enclosed volume, but it presents a larger area of flexible tubing for the absorption of room noises and for the generation of extraneous sounds by the rubbing of the tubes against each other and against clothing and bedding. Comparative tests of double tube models with otherwise identical stethoscopes which have only the single tube to the chestpiece show little or no difference in efficiency when carried out in the quiet environment of a soundproof room, whereas under conditions of ordinary noise the performance of the single tube type is slightly superior. Therefore it would appear that there is no acoustical justification for the double tube versions currently being manufactured *and certainly they are less convenient to* use and to carry.

Earpieces. Aside from the matter of comfort, two factors are of prime importance in the selection of stethoscope earpieces: *leaks* and *occlusion* due to improper fit. *In a recent study[4] of anatomic variations* in the auditory canal marked individual differences in size and configuration were observed. Plastic molds of the canals showed that the earpiece ordinarily rests not in the meatus proper but in the apex of a funnel formed by the concha with its aperture adjacent to the orifice of the cartilaginous meatus (Fig. 3). At this point the concha is distinctly elliptical in shape rather then round, ranging in size in the 10 adults studied from about 6 by 8 mm. to 10 by 14 mm. Probably most of the leaks occur at this point. On

[illegible] of contact) [illegible] the [illegible] large chestpiece, however, [illegible] well as [illegible] to the regular [illegible]

†This hold[s] tr[ue] for sounds in general but [illegible] specific frequency. For example [illegible] long [illegible] scope may tran[smit] [illegible] given frequency bett[er] than [a] shorter stethoscope [illegible] with the resonances dep[ic]ted [in] Fig. 2. But as a rule [illegible] R[ather] they are [illegible] of [illegible] which have little or no [illegible] relationship.

the other hand an earpiece which is too small or which is applied with too great a pressure rests so deeply in the concha that its aperture is partially or even completely occluded by the anterior wall of the cartilaginous meatus Moreover the axis of the concha although generally directed somewhat anteriorly and superiorly showed considerable variation as much as 43 degrees in the vertical plane (angle I in Fig 3) and 33 degrees in the horizontal plane (angle *II*) Thus the angle of direction of earpieces as well as their size and shape would appear to be instrumental in determining the efficiency of stethoscopes

The amount of compliance of the ear structures is uncertain but in many cases a better fit of the earpiece can be achieved by experimentation which allows for these individual variations in the auditory canal Generally earpieces which are larger than those customarily employed are less likely to be occluded and will result in a better acoustical seal

Combinations of these defects no one of which may detract too noticeably from the performance of a given stethoscope

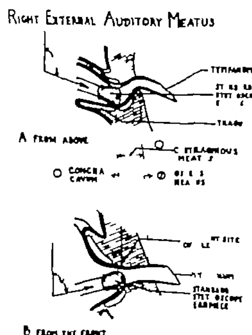


Fig 3 Influence of anatomic variations in auditory canal on the fit of stethoscopes For discussion see text

can add up to gross impairment (e g Nos 9 and 16 in Table I which had small earpieces plus soft gum rubber tubing or Nos 14 16 and 26 which combined the same tubing with excessive length and volume) And the losses caused by some defects are preferential as to frequency long tubing with a rough interior surface attenuates principally the higher pitched sounds whereas losses due to leaks are greatest at the low end of the spectrum Obviously many variables influence the efficiency of a stethoscope Usually more than one factor can be corrected to advantage

Ambient noise

From a practical standpoint the effective efficiency of any stethoscope in transmitting cardiovascular sounds of less than moderate intensity is strictly limited by the level of ambient noise in the examining room In the ordinary busy hospital clinic or office environment there is a more or less constant level of background noise which even though one becomes acclimated and somewhat oblivious to it does interfere with auscultatory examination (although not usually to the degree indicated in the white noise experiment of Table I)

Levels of 60 to 70 decibels as measured on a sound level meter are representative of those encountered in hospital wards[4] and arise from both human and mechanical sources By relatively simple soundproofing measures the ambient noise in an examining room of average size can be reduced to a loudness level on the order of 35 decibels Although that is not a really quiet room by acoustical standards it does provide sufficient reduction of the masking effect of extraneous noise to greatly enhance auscultatory audibility Representative of actual clinical conditions is the measurement of threshold for detection of a diastolic murmur by 40 physician subjects[5] under these two environmental conditions wherein there was an average improvement of over 11 decibels indicating that the same murmur which could be heard in the quiet room had to be increased to more than twelve times the intensity to be audible under the conditions of noise encountered in hospital wards and clinics

experience with such a room

impressive indeed Moreover the grading of intensity of murmurs is also altered for that is in large part a judgment of relative intensities—the signal to noise ratio

Regardless of one s hearing acuity or professional training and experience drastic reduction in ambient noise is one of the most effective means of improving the accuracy and scope of cardiac auscultation

Summary

Comparisons of stethoscopes disclosed surprisingly large differences in the efficiency of transmission of cardiovascular sounds Chief determinants of efficiency are the length of the transmission pathway its total enclosed volume the internal diameter and the physical characteristics of the tubing and especially the integrity of the acoustical seal between the auditory canal and the chest wall Even minimal leaks around ill fitting earpieces in the tubing in the changeover valve or in the chestpiece not only admit ambient noise into the enclosed acoustical system but grossly impair the transmission of sounds

Measurements of stethoscopic audibility of murmurs demonstrate that the efficiency of the average stethoscope in use can be materially increased and that a reduction in the levels of ambient noise commonly encountered in wards and examining rooms results in a significant improvement in auscultatory proficiency

The author acknowledges with gratitude the contributions of several medical student assistants in the Heart Sound Laboratory notably Clarence Davis and Wadly Chapman Mr W W Francis provided technical aid in construction of the artificial precordium and its associated electronic equipment

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Pulmonary hypertension due to myxoma of the right atrium

With special reference to the behavior of emboli of myxoma in the lung

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A myxoma in the right atrium is much less common than one in the left and the diagnosis still presents difficulties. In the past it has been confused with Ebstein's anomaly,[1,2] constrictive pericarditis,[3,4] tricuspid stenosis,[5] carcinoid tumor,[7] and bacterial endocarditis.[8] The diagnostic features of myxoma have been reviewed by Barlow and associates,[9] who mention the frequent occurrence of systemic emboli from tumors on the left side but state that embolism from right atrial myxomas seems not to have been encountered so often. This may be because pulmonary embolism is more often silent. We describe here the case of a patient with a right atrial myxoma in whom the initial symptom was recurrent pleural pain probably due to myxoma emboli which caused pulmonary infarction and finally resulted in pulmonary arterial hypertension. The patient died after removal of the tumor and autopsy revealed wide dissemination of myxoma throughout the pulmonary arterial tree.

Case report

The patient, a 35-year-old housewife, had an attack of pleurisy on the right side in March 1959. No abnormal physical signs were reported in the heart or lungs, but a radiograph of the chest showed an opacity in the right lower lobe which was considered to be an area of resolving pneumonia. The heart was of normal size and configuration. She failed to keep subsequent appointments but was referred again in April 1961 after another attack of pleural pain on the right side. There were still no abnormal physical signs. In January 1962 she complained of tiredness, exhaustion, and progressive exertional breathlessness, and when she attended again in September 1962 a heart murmur was noted for the first time. By this time she was severely incapacitated, being limited to 50 yards of slow walking on the level. She had difficulty in climbing a flight of stairs and was unable to do housework. There was no history of paroxysmal dyspnea, anginal pain, syncope, or swelling of the ankles. She had had a cough since December 1961 productive of mucoid sputum which was frequently stained with blood. There was no previous history of rheumatic fever or chorea, and she had no knowledge of any previous heart disease. She had had two normal pregnancies 7 and 13 years previously.

On examination she was slightly cyanosed and there was early clubbing of the fingers. Her pulse was 90 per minute and regular. The blood pressure was 120/80 mm Hg. Prominent a waves were visible in the jugular venous pulse, and the cardiac impulse suggested right ventricular enlargement. The pulmonary element of the second heart sound was accentuated. Superficial rather scratchy murmurs, at first considered to be exocardial, were audible in mid-systole and mid and late diastole. The murmurs were widely conducted but were maximal in the fourth and fifth left intercostal spaces at the sternal edge. They did not appear to vary either from day to day or with posture or respiration. The lungs were clear. The liver was palpable two finger-breadths below the costal margin, but there was no peripheral edema. There were

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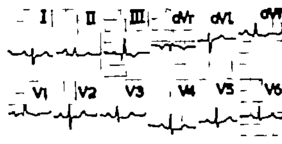


Fig 1 ECG showing right axis deviation and right ventricular enlargement

no varicose veins nor other obvious source of pulmonary emboli There was no pyrexia at any time while she was in the hospital

The electrocardiogram (Fig 1) showed right axis deviation and changes in the precordial series due to right ventricular enlargement The radiograph compared with that taken in 1959 (Fig 2) showed an increase in the heart size with increased prominence of the outflow tract of the right ventricle and the pulmonary arteries There was no left atrial enlargement

A provisional diagnosis of pulmonary arterial hypertension secondary to recurrent pulmonary emboli was made and she was admitted for further investigation Catheterization of the right side of the heart was carried out on Oct 8 1962 No difficulty was experienced in passing the catheter into the right ventricle and pulmonary artery although its course in the right atrium appeared to be unusual and at times during manipulation a sensation that the tip was impinging on a mass was obtained Sampling showed no intracardiac shunt although there was slight arterial oxygen unsaturation (brachial artery 89 per cent femoral artery 88 per cent) The pulmonary capillary venous pressure was normal (5 mm Hg) but there was considerable pulmonary arterial hypertension (52/25 mean 36 mm Hg) When the catheter was withdrawn from the right ventricle to the right atrium a diastolic pressure gradient of 10 mm Hg was recorded (Fig 3) This was due to large a waves (20 mm Hg) in the atrial pressure tracing (Fig 4) The right atrial angiocardiogram (Fig 5) showed an enormous filling defect occupying most of the right atrium The pulmonary artery and its main branches were dilated and passage of the contrast medium through the pulmonary circulation was very slow The results of the other investigations were as follows Hemoglobin 12 8 Gm per 100 ml leukocyte count 6 600 per cubic millimeter erythrocyte sedimentation rate 7 and 14 mm fall in 1 hour total serum proteins 7 2 Gm per 100 ml (albumin 3 9 globulin 3 3) On three occasions the electrophoretic strip showed slightly increased beta 2 and gammaglobulins

A diagnosis of right atrial tumor probably a myxoma was made and the pulmonary arterial hypertension was thought to be due to tumor emboli causing obstructive pulmonary vascular disease

Exploration of the right atrium was carried out by Mr J Leigh Collis on Nov 29 1962 with the aid of extracorporeal circulation and hypothermia A large myxoma attached to the atrial septum in the region of the fossa ovalis was found and removed (Fig 6) After operation the right atrial pressure was high the systemic blood pressure was low and there was arterial oxygen unsaturation Tracheostomy was performed but the patient's condition never became satisfactory She died 27 hours after operation probably from right ventricular failure





Fig 2 Chest radiograph *Top* In 1959 the heart size is normal but there is opacity in the right lower zone due to pulmonary infarction *Bottom* In 1962 there is an increase in the heart size and prominence of the pulmonary artery

Autopsy findings

HEART The heart weighed 285 grams. The superior ... na cava was normal. The right atrium was dilated. The large polypoid tumor which had been removed at thoracotomy and received previously for histologic examination was grayish in color and gelatinous in consistency. This tumor had arisen from the margins of the fossa ovalis and measured approximately 8 by 6 by 4 cm (Fig 6). It was very friable and when handled pieces broke off readily. The tricuspid valve was normal in structure and circumference (12 cm). The right ventricle was greatly dilated but hypertrophy was not obvious. In most places the thickness of the myocardium was only 3 mm but in the region of the infundibulum it was 7 mm. The slightly increased bulk of right ventricular muscle was confirmed by its weight of 75 grams which exceed the upper limit of normal by some 10 grams.[19] The pulmonary valve was normal in structure and circumference (7 cm). There were a few isolated plaques of pulmonary atherosclerosis. The pulmonary vein and left atrium were normal. The mitral and aortic valves were normal in structure and circumference. The left ventricle was 13 mm thick and weighed 145 grams. The origin, course and distribution of the coronary arteries were normal.

LUNGS The lungs felt abnormally firm and when sectioned the appearances were remarkable. Many of the pulmonary arteries from the main lobar branches down to the smallest branches visible to the naked eye were completely occluded by a gray jelly-like substance similar in appearance to the atrial myxoma.

Histology The macroscopic appearances of the myxoma are described in the following section. Sections from the pedicle of the tumor showed no invasion of the atrial myocardium or blood vessels. Myxomatous tissue was however closely applied to the adventitial surface of small coronary arteries and veins.

PULMONARY VASCULAR PATHOLOGY The majority of the muscular pulmonary arteries and some of the pulmonary arterioles were distended and partially or completely occluded by emboli from the myxoma in the right atrium. The material blocking the vessel consisted of spindle-shaped and elongated cells with round or oval nuclei and prominent nucleoli embedded in a loose myxomatous stroma (Fig 7). Some of the cells were binucleate. Frequently a group of these cells formed a syncytium part of which was closely associated with a small vascular channel containing erythrocytes (Fig 7). These blood spaces appeared to be an integral part of the structure of the myxoma and a section through a pulmonary artery occluded by myxoma always included large numbers of them (Figs 8 and 9). The stroma of the myxoma was loose, appearing vacuolated in places. It stained faintly pink with eosin and creamy gray with Van Gieson stain. Special stains described in the following section were helpful when combined with a suitable counterstain of contrasting color in demonstrating the precise extent of spread of the myxoma in the vasculature of the lung.

Many arteries contained eccentric nodular masses attached to the intima of only part of the circumference of the artery. Others were totally occluded by myxomatous emboli. In many instances myxoma could be seen extending from a parent artery into an arteriolar branch (Figs 8 and 9). In some instances a large thin-walled channel filled with erythrocytes was seen within a mass of myxoma (Fig 9). Some of these channels had extremely thin walls lined by the plump myxoma cells but others had thicker walls of collagen fibers. In some arteries a central channel surrounded by rather fibrous myxoma was itself occluded by an embolus of myxoma which contained no collagen (Fig 9). One pulmonary artery contained an embolus of myxoma in which was embedded a fragment of bone marrow (Fig 10); it seems likely that this tissue had been dislodged from the sternum during sternotomy.

The muscular pulmonary arteries occluded by myxomatous emboli were thus ... and

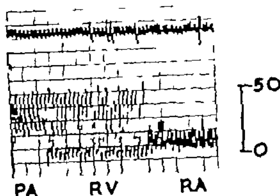


Fig 3 Withdrawal pressure trace from the pulmonary artery (*PA*) and the right ventricle (*RV*) into the right atrium (*RA*). There is pulmonary arterial hypertension and a diastolic pressure gradient of 10 mm Hg as the catheter enters the right atrium from the right ventricle.

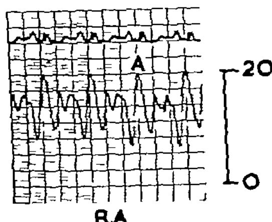


Fig 4 Right atrial pressure trace showing large atrial waves (*A*).

In other instances the media appeared to be actively infiltrated by the myxoma (Fig. 11); the extent of spread of the myxomatous tissue was easily demonstrated by the special stains referred to in the next section. In such areas the internal and external elastic laminae were abnormally thinned and in



Fig. 5. Angiocardiogram (lateral view) showing right atrial myxoma. This is seen as a filling defect circular in outline in the lower right hand corner of the cardiac shadow.



Fig. 6. The myxoma photographed in the operating theater immediately after its removal. Note the white pedicle to the right. The tumor has a glistening gelatinous appearance.

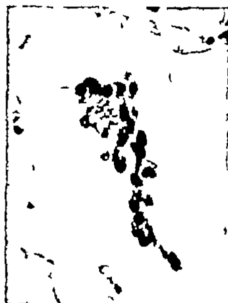


Fig. 7. A small syncytial group of myxoma cells which is closely associated with a thin-walled blood vessel. These cells are embedded in a loose myxoid stroma. (All sections stained for elastic by the Lawson modification of the Weigert-Sheridan method and by Van Gieson's stain.) Magnification ×450.

some places were actually ruptured (Figs. 12 and 13). In numerous sites this process had proceeded to the stage of infiltration of the adjacent adventitia by the myxoma (Figs. 12 and 13). At these places strands of elongated strips of myxoma cells with their long axes radial with respect to the artery could be seen in the sites of total destruction of the media (Figs. 11 and 12). Apart from actual breaks in the media, there was widespread thinning of the media probably brought about by distention of the arterial wall by the mass of myxoma within its lumen.

Some myxoma emboli were found in bronchial arteries (Fig. 14). No myxoma was found in pulmonary capillaries, veins, or lymphatics. No longitudinal muscle had developed in the walls of the pulmonary arteries. No plexiform lesions[14] were seen.

STAINING REACTIONS OF THE TUMOR MATRIX. The finely fibrillar matrix stained very strongly with Southgate's mucicarmine for mucins. The periodic acid-Schiff reagents did not stain the matrix, which fact suggests that neutral polysaccharides were not present. On the other hand, a strongly positive staining reaction was given by Alcian blue, a water-soluble copper phthalocyanin which stains acid mucopolysaccharides of epithelial and connective tissue origin.[15] A positive reaction was also given by Hale's dialyzed iron method, in which colloidal ferric iron is absorbed by such acid mucopolysaccharides and is later demonstrated by the addition of acid potassium ferrocyanide. Unfortunately, this reaction has a low specificity and hence of



Fig. 8 Section of a large muscular pulmonary artery and a thin walled arteriolar branch which is seen running vertically downward. Both the artery and its branch are largely occluded by an embolus of myxoma. Large thin walled blood vessels are present in the embolus. Magnification ×40



Fig. 9 Transverse section of a muscular pulmonary artery occluded by an embolus of myxoma which includes many thin walled blood vessels. One of these vessels is particularly large and has itself become occluded by a fresh embolus of myxoma. Magnification ×50

limited value in confirming the presence of acid mucopolysaccharides in this case. Nevertheless toluidine blue, a dye of the thiazine group, produced metachromasia with the matrix of the myxoma. This phenomenon, in which the absorption spectrum of the tissue-dye complex differs from that of the dye alone, is dependent upon polymerization of the substrate leading to polymerization of the dye. It is characteristic of mucopolysaccharides and related compounds such as chondroitins B and C which occur in heart valves and blood vessels. The development of metachromasia in this case was prevented by initially treating the unstained sections with testicular hyaluronidase. Of the two chondroitins mentioned only type C shows this lability.[illegible] Hence we may deduce that the predominant substance present in the matrix of the myxoma was acid mucopolysaccharide in nature and related to chondroitin C.

Discussion

The clinical features, differential diagnosis and methods of investigation of right atrial myxomas have been discussed previously.[illegible] Although systemic emboli are a prominent feature of left atrial myxoma, the importance of recurrent pulmonary emboli from right atrial myxoma may have been underestimated. It has been said[9] that pulmonary embolism from a right atrial myxoma seems not to have been encountered so often. Gibson and Wood[14] described the case of a patient with right atrial enlargement, a diastolic gradient across the tricuspid valve, and transient



Fig. 10 Part of section of a large muscular pulmonary artery occluded by myxoma. Bone marrow tissue has been included in the embolus. ×100



Fig. 11. Part of transverse section of a muscular pulmonary artery showing infiltration of the myxoma through the media into the adventitia. Note that the long axes of the cells in the break in the media are radial. There is infiltration of the media. Magnification ×150.



Fig. 12. Part of transverse section of a muscular pulmonary artery occluded by an embolus of myxoma. The myxoma has broken through the media to invade the adventitia. Note the frayed elastic laminae at either side of the break in the media. Magnification ×125.

lung shadows whom they believed had tricuspid stenosis due to disseminated lupus erythematosus. It has been suggested[9] that this clinical picture may have been the result of a right atrial myxoma with pulmonary emboli. Emanuel and Lloyd[8] described the case of a patient with pleural pain, lung opacities, and pleural effusion in whom a diagnosis of constrictive pericarditis was made but in whom a large right atrial myxoma was found at autopsy. Death was due to obstruction of the main pulmonary artery by portions of the tumor which had become detached. Several of the small pulmonary arteries were blocked by myxoma tissue but the pulmonary arterial pressure was normal at cardiac catheterization. Kendall and Symonds[9] also described the case of a patient with multiple pulmonary infarcts who was thought to have bacterial endocarditis but who at autopsy was found to have a right atrial myxoma. Paquet[10] described the case of a patient with pulmonary arterial hypertension who was operated on erroneously for mitral stenosis. The patient died suddenly and autopsy revealed a right atrial myxoma with tumor nodules disseminated in the pulmonary vessels. Sudden death during operation from pulmonary obstruction due to dislodgment of portions of tumor has also been described.[14,17] Our patient's initial symptoms of recurrent pleural pain were almost certainly due to tumor emboli causing pulmonary infarction. Many more silent emboli probably occurred during the following 3 years so that serious obstruction to the pulmonary circulation was present by the time the diagnosis was made. It seems likely that pulmonary embolism from a right atrial myxoma occurs more frequently than has hitherto been suspected. It is obviously important, therefore, that the diagnosis be considered in any patient with recurrent pulmonary emboli so that surgical treatment can be instituted before wide dissemination occurs.

Nature of the tumor. The importance of this case is that it has afforded us an opportunity of studying the behavior of dislodged fragments of an intracardiac myxoma at a distant site. There has long been a difference of opinion whether this tumor is a true neoplasm or a thrombus showing myxomatous degeneration. It



Fig. 13 Part of transverse section of a muscular pulmonary artery showing extension of the myxoma through the media into the adventitia. Note the small blood vessel in the myxoma. Magnification × 75

seemed likely that examination of the lungs of this patient might provide evidence to support one theory or the other since one would anticipate the possibility of differentiating the appearances of metastatic spread of a neoplasm to the lung from the well known appearances of pulmonary thromboembolism

In recent years most authors have supported the idea that the myxoma is truly neoplastic. The arguments advanced are that the classic atrial thrombus is smooth whereas the myxoma is lobular and even villous[11] The typical thrombus is usually firm granular and opaque whereas the myxoma is semitransparent gelatinous and greenish[18] Atrial thrombi often show lamination a feature never found in the cardiac myxoma[19] A thin pedicle is said to be much more characteristic of the myxoma than the thrombus. Intracardiac myxomata are common in the atria but rare in the ventricles where thrombi are common[19]

Histologically the presence of stellate cells in syncytial groups and the peculiar mucinous stroma is characteristic of the myxoma but quite different from the structure of a thrombus. Certain features which all admit are of no value in distinguishing myxoma from thrombus since they commonly occur in both lesions include the presence of small blood vessels hemosiderin chronic inflammatory cells and macrophages. The protagonists of the neoplastic theory point out that the existence of typical thrombus on the surface of an intra atrial mass does not imply that such a lesion is a thrombus for thrombosis commonly occurs on the surface of a true myxoma. This list of differences between the macroscopic and microscopic appearances of the intracardiac myxoma and thrombus is impressive and suggests that the myxoma is a true neoplasm

The behavior of the embolic fragments of myxoma in the lung in this case tends to support this point of view. If the mass in the right atrium were merely a thrombus one would anticipate that embolic fragments of it in the lung would be organized and present the well known appearances of recurrent pulmonary thromboembolism. In fact the appearance and behavior of the embolic fragments of myxoma emboli were totally different from this. Indeed the media of the muscular pulmonary arteries was breached by the cells of the



Fig. 14 Transverse section of a bronchial artery containing an embolus of myxoma. Magnification × 100

emboli (Figs. 11-13). However, these appearances might be held by some not to be the incontrovertible proof of low-grade malignancy that they seem to be initially. The widespread impaction of emboli had produced pulmonary arterial hypertension which may have been capable of forcing out myxoma emboli through the branches and even walls of small thin-walled pulmonary arteries. Many such foreign bodies may be extruded through the walls of pulmonary arteries, such as cotton wool fibers inadvertently introduced by intravenous injection.[22] Furthermore, in the present case we have histologic evidence that emboli of myxoma were forced into the bronchial arteries through bronchopulmonary anastomoses, presumably as a result of pulmonary hypertension (Fig. 14).

In any consideration of the nature of the cardiac myxoma it seems pertinent to recall the close similarities between the gross and histologic appearances of the atrial myxoma and papilliferous tumors of heart valves. The distinctive features of the myxoma are all shared by these villous gelatinous fronds on cardiac valves. Even the matrix of them has identical tinctorial properties in staining only faintly with PAS but in giving strongly positive reactions for acid mucopolysaccharides.[23] Furthermore, as in the present case of intracardiac myxoma, the staining reactions of papilliferous tumor of cardiac valves are prevented by initial treatment with hyaluronidase.[23] Clearly, whatever etiological factors are advanced to explain the appearance and development of papilliferous tumors of heart valves must be seriously considered in the case of intracardiac myxomas of similar appearance. Here we come to the same impasse. Some authors[24] believe the valve tumors to be hamartomas with only a limited capacity for growth. Others[1] are of the opinion that they are entirely thrombotic in origin and development. Pomerance[1] thinks it likely that they originate in and grow from the close approximation of Lambl's excrescences, which are themselves formed by the organization of small deposits of fibrin on sites of endothelial damage.[25] Nevertheless, our study of the present case has left us with the strong impression that the cardiac myxoma is a true neoplasm of limited invasiveness on the grounds that fragments of it forming pulmonary emboli are not organized like thromboemboli but have some capacity for infiltrating the walls of the pulmonary arteries into which they have become impacted.

Nature of the pulmonary hypertension. Myxomata of the atria are a rare cause of pulmonary arterial hypertension. Since they are usually situated in the left atrium the elevated pressure develops by the same mechanism as in mitral stenosis, that is, secondary to a rise in left atrial blood pressure. For instance, in the case of Towers and Newcombe[4] there was a left atrial hypertension of 61/21 mm. Hg and a pulmonary arterial hypertension of 106/54 mm. Hg. In this more common situation the pulmonary blood vessels and parenchyma will be expected to show those structural features associated with coexistent hypertension in the pulmonary arteries and veins.[2]

In contrast, the pulmonary hypertension in this case was embolic in origin and the left atrial and pulmonary venous blood pressures were normal. The majority of the muscular pulmonary arteries did not show medial hypertrophy such as occurs with pulmonary hypertension secondary to left atrial hypertension but medial atrophy secondary to occlusion of these vessels by myxoma emboli.

Summary

A 35-year-old woman developed a pulmonary arterial hypertension of 52/25 mm. Hg with a diastolic pressure gradient of 10 mm. Hg across the tricuspid valve. Radiography revealed shadowing in the right lower lobe, and angiocardiography showed an enormous filling defect in the right atrium. A diagnosis of pulmonary hypertension with underlying obstructive pulmonary vascular disease complicating a myxoma of the right atrium was made successfully, and the mass was removed surgically. The patient died of congestive cardiac failure after the operation. The pulmonary arteries were found to be occluded by emboli of myxoma which had actively infiltrated the media. The appearances were totally unlike those of recurrent pulmonary thromboembolism. This capacity for limited invasiveness leads us

to believe that the cardiac myxoma is a true neoplasm and not a degenerate thrombus

We gratefully acknowledge the help of Mr J Leigh Collis F R C S who performed the operation Dr J C A Kanon Consultant Clinical Physiologist and Dr M K Alexander Consultant Pathologist

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Comparison of human and computer electrocardiographic wave-form classification and identification

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The automatic diagnosis of electrocardiograms has recently reached the stage of practical application with the appearance of analog-digital conversion equipment especially designed for this purpose the appearance of digital computers with sufficient capacity and the possibility of telephone line transmission of electrocardiograms (ECGs) between hospitals and computation centers

Hitherto the principal basis for automatic interpretation has been a point recognition technique[1-8] which recognizes the P QRS and T waves of the electrocardiogram Thereafter the amplitude and duration of the P QRS and T waves and certain durations or other abstracted geometric relationships between any two of them have been measured so that statistical matrices containing these isolated values could be made the basis for diagnostic evaluation

The present paper however describes a different method for the automatic interpretation of the electrocardiogram in which a multiple adaptive matched filter technique is used to recognize wave form patterns We have previously described a number of details of this method[4-6] Among its theoretical advantages are the a priori rejection of a much smaller amount of information in the electrocardiographic wave form apparent similarity to human interpretation processes possibilities for self programming and the straightforwardness of the computational aspects due to lack of the need for Fourier[7] or other transformations out of the time domain

The present study was designed to document the validity of some of the advantages listed above by observing the accuracy with which QRS complex wave forms were identified when compared with known previously diagnosed complexes and also by comparing human and machine classification of these known reference complexes into categorical groups

Method

Filters The essence of our approach consists of the use of multiple adaptive matched filters Space for a sufficiently large number of such filters is made part of the computer program Each filter is

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initially blank open to any time normalized signal wave form. When the filters are thus open or adaptive the first signal coming along will enter the first available filter and thereby impress its own wave form on the filter. Thereafter any subsequent signal cannot enter that filter unless its wave form has a cross correlation coefficient with the first wave form exceeding a threshold value. In this paper this value has been set at 0.7. If a second signal's correlation coefficient exceeds 0.7 it too will enter the first filter and that filter's prime pattern thereafter adapts or changes to become the mean value between the two signals which have entered it. If a third signal should fail to have a correlation coefficient of 0.7 with the first filter in its new form then that signal would enter a second blank filter thereby starting a new grouping. This process continues until all the signals have been classified as desired. The higher the correlation coefficient threshold is set the greater will be the number of filters used and the finer will be the categorization.

At any time that useful filter conformations are encountered the filters can be fixed in permanent form so that consistent identification will be performed. It is important to clearly distinguish between the two operating conditions or modes of our multiple matched filter program.

The first or adaptive mode is used to form a *classification* of a large set of wave forms by adaptively categorizing the entire range of wave forms into groups of similar patterns. Each group consists of similar wave forms with a certain amount of intragroup variability permitted whereas the differences between groups are more marked. Thus in this way the adaptive mode forms a classification.

The second or fixed mode utilizes an already formed set of fixed matched filters to *identify* a patient's unknown wave form by comparing it with the fixed library of diagnostic patterns. Each fixed filter or pattern has a diagnostic name or number. When the unknown wave form shows high correlation with a particular fixed pattern

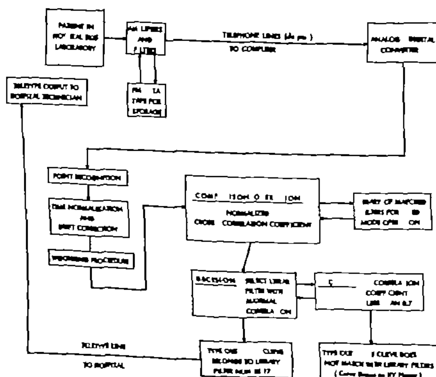


Fig. 1 Fixed mode flow diagram

it is thereby identified or named. Thus in this way the fixed mode performs in identification.

Preliminary processing of data. The X, Y, and Z component electrocardiograms of the three-dimensional vectorcardiogram from 21 patients were recorded on FM tape for 10 seconds at a speed of 30 inches per second (ips) at the Boston University Medical Center. Prior to analog-digital conversion, background noise superimposed on the tracings was eliminated as much as possible by electronic filter circuits.

These analog data were then converted into digital form at a sampling rate of 600 data points per second using a GE 225 digital computer with analog-to-digital conversion capability. Further analysis was carried out on an IBM 7090 digital computer as indicated in the fixed mode flow diagram in Fig. 1. Before comparisons were made the following procedures were carried out to facilitate computation: point recognition, time normalization, and drift correction.

After point recognition of the QRS complex, the total duration of that complex was divided into 30 equal intervals (time normalization). Drift correction was accomplished by setting the level of both the starting and the terminal points to zero. These QRS complexes were used to test the pattern recognition program and will be referred to hereafter as patient QRS complexes.

CROSS CORRELATION. As the basis for comparison with the undiagnosed patient QRS complexes, previously diagnosed and digitized component vector electrocardiograms were selected; these were representative of many different QRS patterns. These reference patterns, 55 in number, will hereafter be called library QRS complexes. The determination of the degree of similarity between any patient QRS complex to be identified and any one of the library QRS complexes was obtained by calculating the cross-correlation coefficient of the amplitude values of the 31 points of the two time-normalized QRS complexes as shown in Fig. 1. The computer was directed to detect the library QRS complex with the largest cross-correlation coefficient over the value of 0.7

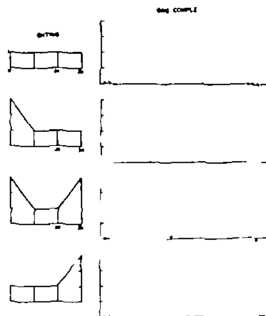


Fig. 2. Examples of weighting method. On the left the weights applied to various parts of the time-normalized QRS complex are illustrated. On the right are actual digital values of a particular QRS complex subjected to these different weightings. Open circles represent unchanged value; solid circles show weighted values.

and to type out the index number of that library QRS complex.

WEIGHTING TECHNIQUE. According to accepted medical criteria, the initial or terminal parts of the QRS complex are of special importance, for example, in cases of myocardial infarction or bundle branch block. We investigated this aspect of pattern recognition by emphasizing the initial or terminal portions of the actual QRS complexes under study by means of a weighting technique. The amplitude values of the initial or terminal portions of the QRS complex to be weighted were amplified in the various proportions indicated in Fig. 2. Weighting was decreased or increased gradually so that discontinuities in the wave form did not result. The initial, final, or both parts of the library QRS signals were also weighted by the computer. Then the multiple matched adaptive filter method was used to form new fixed filters from these weighted signals for the next pattern identification procedure. Comparison was then made between the

weighted pattern identification performed by the computer and the human pattern identification

ADAPTIVE MACHINE HUMAN COMPARISON The 55 library QRS signals were automatically classified into 10 groups by the 7090 computer making use of the multiple adaptive matched filter program. The correlation factor of 0.7 was again used to determine whether the given QRS complex would enter a certain grouping of complexes. Next each of 10 human observers were instructed to classify quickly the 55 QRS signals into 10 or 11 groups. They were not aware of the results of the machine classification. Each observer was allowed to make only one original decision on each pattern and each pattern was presented to him in the same order as it was presented to the computer. The human and automatic computer classifications were then compared.

The 55 library QRS patterns were picked up in random order and were classified by computer 10 times by the multiple adaptive filter technique. The reproducibility of the classification on these 10 runs was then determined. One human observer was then also asked to classify the 55 library patterns 10 times, random order presentation again being used. An analysis was then made of the similarity between human and computer classification reproducibility.

Results

Fixed filter mode Sixty three patient QRS complexes to be automatically identified were processed as indicated by the examples shown in Fig 3. The first column indicates the patient complex to be identified and the second column indicates the pattern index number and correlation coefficient of the library QRS complex with the maximum correlation coefficient over 0.7. The third column shows the same information as the second except for the use of 3 1 1 weighting, the fourth column 3 1 3 weighting and the last column 1 1 3 weighting.

In the identification without weighting (column 2) the patient QRS complexes are generally similar in shape to the selected library QRS complexes although not neces

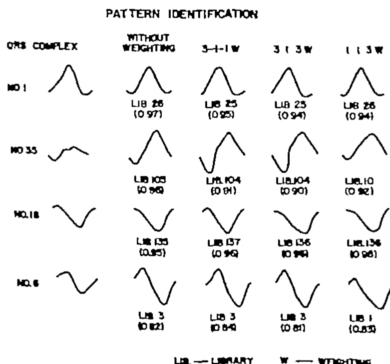


Fig 3 Example of automatic pattern identification in the fixed filter ...

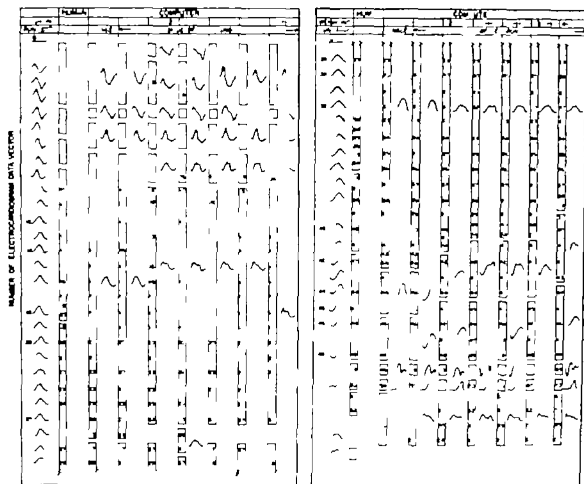


Fig 4 Comparison of a pattern classification formed by human observers with pattern classification automatically formed by the computer program in its adaptive mode under a variety of weighting conditions

sarily identical with respect to amplitude because only correlations were used In the correlation technique of course one cannot distinguish between two curves of the same over all shape but of different amplitude As shown in Fig 3 the shape of the QRS complex in column 1 was in most respects similar to that in column 2

Table I shows the summarized results of fixed mode pattern identification of 63 patient QRS complexes according to the available library (55) QRS patterns Row 1 indicates that of the 63 patient QRS complexes 49 were identified well and 11 were identified imperfectly by qualitative electrocardiographic[1] criteria Three were not identified with a correlation coefficient over 0 7 without weighting When the 60 patient QRS complexes which gave correlation with library complexes over 0 7 when unweighted were subsequently re-evaluated with weighting as indicated in Rows 2 3 and 4 improved identification resulted again according to qualitative electrocardiographic judgment

Adaptive pattern classification mode After the 55 library complexes had been classified by the computer on the basis of the multiple adaptive filter scheme and similarly classified by 10 human observers the results of both procedures were compared There was a striking degree of similarity in the results of the human and machine classification as shown in Fig 4 Most of the differences depended upon the variability of classification of patterns which were borderline between two similar groups Similar intra observer and inter-observer variability has been noted in ordinary clinical ECG interpretations[4] Of the 10

human observers 5 were physicians experienced in electrocardiography and 5 were engineers without such knowledge. No significant differences in the classification was noted between the two types of observers under the conditions of the experiment.

When the 55 library QRS complexes were classified by the multiple adaptive filter technique with varying weightings it was found that weighting increased the resemblance of the unweighted pattern classifications of the 10 human observers suggesting that the human observers did indeed weight some part of the QRS complexes unconsciously.

To determine the influence of the order of presentation in which the various library QRS complex patterns were considered by the computer these were classified in random order 10 times by the computer. The results are plotted in Fig. 5 A. The abscissa indicates the number of the classification run whereas the ordinate indicates the number of complexes which were differently classified in each run when compared to the mode for the 10 successive runs. The irregular curve of Fig. 5 A indicates that the ordinate deviation from the mode is a random variable as expected since the computer memory is erased before each new adaptive mode classification run. This memory erasure did not occur with the human observer; indeed he seemed to stabilize his pattern classification scheme with successive runs. Figure 5 B shows the gradual progressive reduction of deviation from his modal classification.

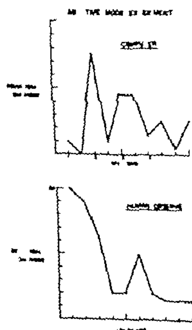


Fig. 5 Variability in pattern classification with 10 successive independent runs for (A) computer adaptive filter mode and for (B) human observer

Table 1 Summarized results of pattern identification experiments in fixed mode

	Fixed mode pattern identification		
	Well classified	Imperfectly classified	Correlation coefficient below 0.7
No weighting	49	11	3
3-1-1 Weighting	59	1	Omitted
3-1-3 Weighting	56	4	Omitted
1-1-3 Weighting	58	2	Omitted

Discussion

The automatic interpretation of electrocardiograms has thus far been largely based on a point recognition technique which measures the amplitudes and durations of the electrocardiographic tracings and then gives a pattern classification derived from a few such parameters. Although the point recognition technique effectively gives a certain amount of information about a tracing, pattern recognition using the correlation multiple adaptive filter and fixed filter techniques described in the present paper has revealed the possibility of utilizing the entire curve. In the present study the library QRS complexes were used as fixed filters. It should be emphasized that this [illegible] a somewhat arbitrary procedure which will be replaced as further material and experience are gathered by developing filters for this purpose through the use of the multiple adaptive matched filter technique. After appropriate weighting [illegible] the passage of many thousands of el[illegible] tracings have revealed the most co[illegible] and clinically useful diagnost[illegible] the multiple ad[illegible]

or fixed at this point and used thereafter for clinical diagnosis much as the library patterns were used in the present paper This approach permits the characterization of most of the information in the signal by single index numbers of standard pattern codes as was done in the case of the patient library comparisons in this paper

The combination of the correlation multiple adaptive and fixed filter techniques with the point recognition techniques will of course give a still more exact precise interpretation The opportunity in the present program for weighting made for further flexibility in developing pattern classification more consistent with previous clinical experience and usefulness The extension of these techniques to the P waves ST T segments and the T waves will make for further specificity and clinical utility

Summary

A program for the automatic interpretation of the QRS complex by pattern recognition techniques has been described Considerable similarity to human pattern recognition both classification and identification has been demonstrated particularly with the use of selective weighting of different portions of the QRS complex The method also initially rejects much less information from the input curve than do techniques based only on point recognition particularly since there is no need for transformation of the signal out of the time domain We believe that the described method extended and combined with other techniques holds great promise for automatic interpretation of the electrocardiogram by means of digital computation

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An extrarenal action of mercurial diuretics

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The studies to be reported herein were designed to determine whether mercurial diuretic agents exert an influence on body water exclusive of their effect on the kidney The experiments were prompted by the clinical observation that the rate of flow of edema fluid through Southey tubes was considerably increased after the intravenous administration of mercurial diuretics Likewise an increase in the rate and duration of flow of ascitic fluid through a trocar wound in the abdominal wall was noted if the patients were given injections of mercurial diuretics after paracentesis These responses were seen to occur promptly after the administration of the drug and suggested an extrarenal action of the mercurial agents

Immediately after the intravenous administration of mercurials there is often a decrease in the volume of urine which persists for 10 to 40 minutes[1] This initial antidiuretic effect may be attributed to vascular reactions within the kidney[1-3] but the subsequent diuresis occurs at a time which is consistent with mobilization of fluid from the extracellular space Mercury is bound quite rapidly to protein[4,5] and labeled merallunde was shown to leave the circulation promptly with 20 to 50 per cent being distributed in extrarenal tissue The hypothesis that mercurial diuretics may have an effect on the protein binding of extracellular water seems quite likely Previous investigations of hemodilution after the administration of mercurial diuretics have resulted in conflicting opinions[6-9] However experimental studies by Threefoot[10] clearly demonstrate an extrarenal action by merallunde on the uptake and excretion of vital blue dyes from intradermal injection sites If mercury in mercurial diuretics causes any significant change in the binding of water in tissues an increased rate of flow of lymph should be observed after the administration of mercurial diuretics

Methods and procedures

Twelve normal dogs were anesthetized with intravenously administered pentobarbital (25 mg per kilogram) and studied in the supine position The thoracic duct was isolated in the neck and cannulated with polyethylene tubing The rate of flow of thoracic-duct lymph was determined by serial collection in graduated glass tubes for 5 minute intervals before and after the administration of mercurial diuretics and other drugs Arterial blood pressure was measured directly by means of an indwelling arterial catheter connected to a mercury manometer and venous pressure was obtained in the inferior vena cava through a catheter attached to a water manometer Respirations and pulse were

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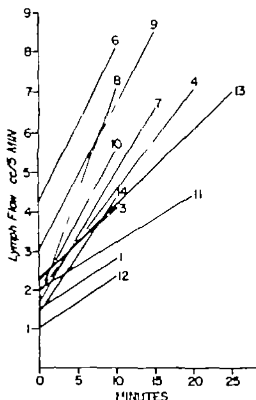


Fig 1 Changes in lymphatic flow after organomercurials Each experiment is identified by its number at the terminus of a line connecting the point at zero time representing the average control flow with the maximal lymphatic flow after the injection of an organomercurial The abscissa indicates the time in minutes after injection at which the maximal flow occurred

counted for a full minute during each of the 5 minute periods of basal observation and continuously during experimental observations An indwelling catheter was inserted into the bladder to obtain urine at 15 minute intervals and was clamped between collections

Five dogs with intact kidneys (Experiments 1 3 4 6 and 7) and one bilaterally nephrectomized dog (Experiment 14) were given 2-c c injections of meralluride One dog received 2 c c of mercaptomerin (Experiment 13) Multiple small injections of meralluride containing 0 0008 Gm of mercury per kilogram of body weight were given in two experiments (Experiments 11 and 12) In one experiment (Experiment 8) the dog was given alternating injections of pentobarbital and bemegride in doses sufficient to cause wide variations in respiratory rate and in two separate experiments (Experiments 9 and 10) epinephrine was given as 1 10 000 solution in doses sufficient to cause wide fluctuations in arterial and venous blood pressures After basal conditions had been re established the animals were given 2-c c injections of meralluride and variations in *lymphatic flow as well as fluctuations in* respirations and blood pressures were compared to those previously recorded in the same dog during respiratory and cardiovascular stimulation respectively All drugs administered during these experiments were diluted to 10 c c with isotonic saline and given slowly (3 to 5 minutes) by vein

Results

The changes in the rate of flow of lymph after mercurial diuretics are summarized *in Table 1 and in Fig 1 Experiment 2* was complicated by purposeful overhydration which resulted in nonphysiologic circumstances and the data are therefore eliminated from the study The dog in Experiment 5 died immediately after administration of pentobarbital In the other 12 experiments a total of 69 measurements of lymphatic flow for 5 minute periods during control observations was made Five measurements were eliminated be

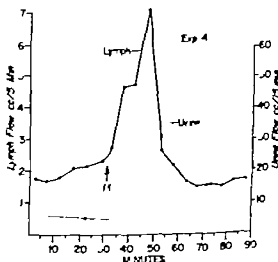


Fig 2 Changes in thoracic-duct lymphatic flow and urinary flow The effect of injection of meralluride on lymphatic and urinary flow is shown The injection period is indicated by an arrow The increased rate of flow of lymph precedes the change in flow of urine as it did in all experiments

*Table I. Flow of lymph before and after mercurial diuretics**

Experimental number	Control lymph flow (c.c./5 min.)		Maximum lymph flow (c.c./5 min.)	Time of maximum lymph flow (min.)	Maximum control
1	1.5	(9)	7.8	10	1.86
3	2.3	(6)	4.1	10	1.78
4	2.0	(6)	7.1	20	3.55
6	4.2	(6)	8.1	10	1.92
7	1.[illegible]	(5)	6.6	15	3.88
8	1.7	(6)	7.1	10	4.17
9	3.0	(7)	8.5	15	2.83
10	2.0	(8)	3.[illegible]	10	2.75
11	3.0	(5)	4.4	—	1.46
12	1.0	(4)	2.3	—	2.30
13	2.2	(4)	7.0	25	3.18
14	1.4	(3)	4.3	10	3.07
Average	2.2		5.7	13.5	2.73

*[illegible]

cause the necessity for re-establishing effective levels of anesthesia altered basal conditions. The other 64 control measurements were considered to represent rates of lymphatic flow under basal experimental conditions. The average control rate for each experiment is shown in Table I. The number of 5 minute intervals measured in each case is shown in parentheses. The range of values is not shown, but lymphatic flow in each experimental animal was observed to be remarkably constant during control observations. The greatest difference between the highest and lowest rate in any single experiment was 0.8 c.c. per 5 minutes, with an average variation in all experiments of only 0.5 c.c. per 5 minutes. The time between the injection of the mercurial diuretic and the maximal rate of flow of lymph is shown for all experiments except those in which multiple small doses were given (Experiments 11 and 12). The flow of thoracic-duct lymph was consistently increased after the injection of mercurial diuretics. The magnitude of this increase is shown in the last column of Table I as a ratio of maximal flow: control flow. The increase in flow ranged from 1.46 to 4.17 times the control rates, with the average being 2.73.

The data from the experiment illustrated in Fig. 2 are presented as being representative of the 12 experiments in this study. During six periods of control observation, the flow of thoracic-duct lymph varied from 1.8 to 2.4 c.c. per 5 minutes (average 2.0). After injection of 2 c.c. of meralluride in 8 c.c. of saline, lymphatic flow began to increase immedi-

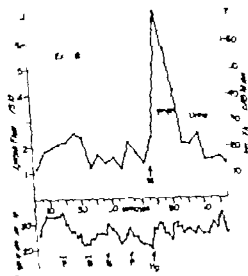


Fig. 3. Effect of [illegible] respiratory rate on lymphatic flow. The [illegible] in respiratory rate after injections of pentobarbital (P), [illegible] (B), and meralluride (M) [illegible]. Although there was no consistent effect on lymphatic flow with rather marked changes in respiratory rate, there was a brisk increase in flow after meralluride.

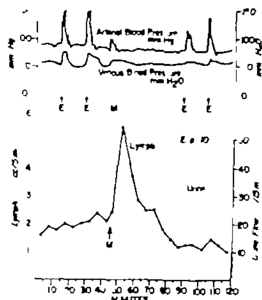


Fig 4 Effect of variation in arterial and venous pressures on lymphatic flow These data show no changes in lymphatic flow as a result of changes in arterial and venous pressures induced by epinephrine (*E*) The administration of meralluride was followed by a 2 5 fold increase in lymphatic flow

ately and by 20 minutes after the initiation of the injection a 3 55 fold increase above control rates was present After an additional 10 minutes the rate of flow had decreased to the control range and remained at that level The flow of urine showed no detectable change until the second collection period (15 to 30 minutes) after the injection and maximal diuresis occurred during the subsequent 15 minute collection period

The administration of the mercurial diuretics was occasionally accompanied by an increase in respiratory rate In order to study the effect of respiratory variation on lymphatic flow after organomercurials the dog in Experiment 8 received pentobarbital and a respiratory stimulant (bemegride) and the changes in respirations and lymphatic flow were compared to those recorded after a subsequent injection of meralluride The results are shown in Fig 3 It is apparent that the change in the rate of flow of lymph after organomercurials cannot be attributed to changes in respiration The relationship of lymphatic flow to subsequent diuresis is again demonstrated

The effect of changes in arterial and venous pressures on lymphatic flow is shown in Fig 4 Elevation of arterial and venous pressures induced by epinephrine did not cause significant alterations in lymphatic flow The injection of meralluride on the other hand was followed by a typical brisk rise in the volume of thoracic-duct lymph in association with only a slight increase in pressures Although lymphatic flow gradually increased during the initial 40 minutes of the experiment there was no prominent change in the rate of flow until the mercurial diuretic was given Maximal flow after the organomercurial was 5 5 c c per 5 minutes or 2 75 times the average flow rate during the eight preceding 5 minute periods

The usual clinical dose of mercurial compounds contains 0 0008 Gm of mercury

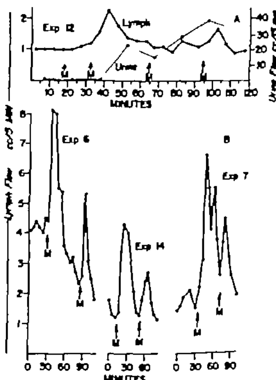


Fig 5 *A* Effect of repeated small doses of meralluride on lymphatic flow The first and third injections produced no detectable effect whereas the second and fourth injection were followed by significant rises in lymphatic flow The increase in urinary output is seen to follow the rise in lymphatic flow *B* Effect of repeated injections of meralluride (2 ml each) on lymphatic flow In each instance there was a rise in lymphatic flow although the magnitude of the second response was less than that of the first one

per kilogram of body weight This dose was administered repeatedly in Experiments 11 and 12 Fig 5 *A* shows the results in a 14 7 kg dog of four intravenous injections each of which consisted of 0 3 c c of meralluride (12 mg of mercury) diluted in 10 c c of saline The initial injection was followed by minimal changes in lymphatic flow but a more prominent change was noted after the second dose Ten minutes after the second injection lymphatic flow had increased 2 3 fold The third injection had no appreciable effect The final injection was followed by a rise in rate of flow to 1 7 times the control Similar data were obtained in Experiment 11 in which two initial injections of meralluride in comparable doses were associated with only slight changes in flow but a more prominent rise occurred after the third injection (1 5 times control flow) Data shown in Fig 5 *B* are from three experiments in which two injections of meralluride (2 c c each) were given The response to these larger doses was of proportionately greater magnitude than those shown in Fig 5 *A* In each instance the second injection of 2 c c was followed by a prompt but smaller change in flow than that after the initial injection The effect of organomercurials on the rate of lymphatic flow seems to be a dose related phenomenon with diminished response to repeated injections

Discussion

Intravenous administration of organic mercurial diuretics to anesthetized dogs resulted in a brisk rise in lymphatic drainage from the cannulated thoracic duct This observation might be explained by several mechanisms Mechanical factors such as muscle activity peristaltic activity and respiratory movements have been studied in these experiments and no influence on rates of lymphatic flow was attributable to these mechanisms At no time was the injection of a mercurial agent associated with detectable tremor or other muscular movements Peristaltic activity of the intestine was not recorded directly but auscultation over the abdomen detected no increase in bowel sounds during or after the injections of mercurials Furthermore Jackson[3] noted an inhibitory action of the intestinal contractions of dogs by mersalyl Another possible explanation is changes in permeability or peristaltic activity of the lymphatic vessels No direct observations were made on these phenomena but some indirect evidence was obtained by the use of epinephrine which leads the authors to minimize the role of changes in function of the lymph vessels themselves in causing the results obtained in these experiments A third possible explanation of these findings is that there was an increase in capillary filtration with resultant increase in lymphatic flow We do not believe that this was an important factor in these observations since there were no changes in lymphatic flow after rather marked changes in arterial and venous pressures Furthermore postulating an increased capillary permeability as a result of organomercurials is unappealing in view of the enormous transcapillary exchange of water and crystalloids under normal circumstances [11] The fourth possibility is that there is a change in the binding of intercellular water as a result of the action of mercurial diuretics If mercury by its tendency to combine with proteins alters the physical nature of tissue water binding one would expect mobilization of interstitial fluid The findings reported by Threefoot[10] are in agreement with these conclusions

Although the onset of increased flow of lymph occurs immediately after the administration of mercury there is a delay of 10 to 25 (average 13 5) minutes before the peak flow of lymph is attained This lag time compares well with the time required for substances injected directly into peripheral lymphatics in dogs to appear in thoracic-duct lymph Likewise the maximal flow of lymph after organomercurials consistently precedes the onset of diuresis and the maximal flow of urine occurs 30 to 45 minutes after the peak flow of lymph Although the direct effect of mercurials on the kidney is well established [12] the mobilization of fluid from the tissue would contribute significantly to the diuresis

Maverson and LeBrie[13,14] have shown augmented renal lymph flow in dogs under a wide variety of circumstances including the administration of meralluride However our observation that a nephrectomized dog (Figs 1 and 5 *B* Experiment 14) re

sponded with the same order of increase in flow of thoracic duct lymph as did normal dogs would exclude the kidneys as a major source of the increase in lymph observed in these experiments

The absolute volume of increased lymphatic flow after mercury is in itself not of sufficient magnitude to influence the diuretic response However it would be expected that a much greater mass of water if freed from tissue binding by mercury would return to the circulation through the venous system Although no observations were made on edematous states it is conceivable that even larger amounts of fluid would be released by the action of mercurials in the presence of excessive tissue fluid Indeed the clinical observations mentioned in the introduction of this paper would suggest an exaggerated response *in the presence of edema* Conversely earlier unpublished observations in hydropenic dogs did not reveal an augmented flow of lymph after injections of mercurials

Summary and conclusions

An extrarenal action of mercurial diuretics has been demonstrated After the intravenous administration of mercurials there is a consistent increase in the flow of lymph Since this phenomenon is shown not to be secondary to mechanical factors which are known to alter lymphatic flow we postulate that mercury acts by altering water binding in tissues Water mobilized from the interstitial compartment enters the circulation and thus may augment the primary renal action of mercury in effecting diuresis

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Case reports

A new form of right ventricular outflow obstruction

Case report

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Obstruction to pulmonary blood flow may result from a number of congenital cardiac anomalies. Pulmonary valvular stenosis, infundibular stenosis, peripheral pulmonary artery stenosis, and pulmonary valvular atresia are the more common of these lesions. The present case represents a form of obstruction of the pulmonary outflow tract which apparently has never been reported in an otherwise normal heart.

Case report

The patient was an 8 year-old white girl who was hospitalized for elective repair of a congenital heart lesion diagnosed as pulmonary valvular and infundibular stenosis. The lesion had been noted shortly after birth. Growth and development had been slow, but he had no notable symptoms until 4 months prior to admission, when she complained of ill-defined anterior chest pain, dyspnea on exertion, easy fatigability, and episodes of weakness and pallor.

Despite a full term gestation, the child weighed only 4 pounds and 10 ounces at birth. Her mother had experienced no illness during pregnancy. A 9 year-old brother and a maternal grandmother had heart disease of unknown type.

Physical findings were essentially normal except for poor physical development and abnormal cardiac findings. The apical cardiac impulse was palpated in the fourth left intercostal space medial to the midclavicular line. There was a prominent right ventricular parasternal thrust which was heaving in character. A systolic thrill was palpable in the first, second, third, and fourth left intercostal spaces parasternally and in the suprasternal notch. The first heart sound at the apex was accentuated. There was a Grade 4/4 systolic ejection murmur which was harsh, long, and crescendo-decrescendo in character and of maximal character and maximal intensity in the second left intercostal space parasternally. The murmur was preceded by a systolic ejection click which was audible only during expiration in the second left intercostal space. This murmur was transmitted widely into the neck, infraclavicularly on the left, and parasternally toward the cardiac apex and into the back. The second sound at the cardiac base was single and audible only over the aortic area. The electrocardiogram (Fig. 1) revealed marked right axis deviation and a qR pattern in Lead V1 with sagging of the S-T segments and T wave inversion, and deep S waves extended over the entire left precordium. This electrocardiogram was interpreted as compatible with severe right ventricular hypertrophy with strain. A chest roentgenogram revealed a normal sized heart, right ventricular enlargement, a prominent pulmonary artery segment, and clear peripheral pulmonary lung fields (Fig. 2). A clinical diagnosis of severe pulmonary valvular stenosis was made.

Cardiac catheterization revealed a systolic pressure gradient of 100 mm. Hg across the pulmonary valve and no evidence of an intracardiac shunt.

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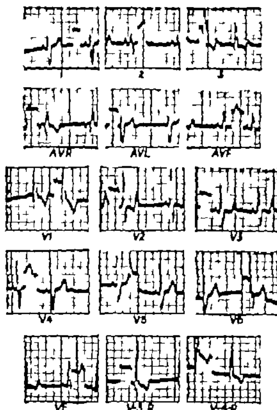


Fig. 1. Electrocardiogram demonstrating severe right ventricular hypertrophy and strain. The presence of q waves in Lead V3R, V1, and V2 differentiates severe right ventricular hypertrophy from complete right bundle branch block.

Selective cineangiocardiography demonstrated a systolic jet into the dilated main pulmonary artery. The infundibular area of the right ventricle appeared to be narrowed. The final preoperative diagnosis was pulmonary valvular and infundibular stenosis.

Under extracorporeal circulation and Fluothane anesthesia the right ventricle was opened. The pulmonary valve was normal and there was slight infundibular muscular stenosis. Just above the crista supraventricularis was a valvular structure which consisted of a large thickened posterior leaflet (2.8 by 1.2 cm.) adjacent to the septum and a smaller anterior leaflet (1.0 by 0.9 cm.). Both leaflets were fixed to the myocardium by a rim of dense fibrous tissue and had multiple chordae tendineae which attached to both septal and mural papillary muscles as well as smaller attachments with the chordae of the normal tricuspid valve below (Fig. 3). The tricuspid valve appeared to be normal. This entire valvular structure was excised along with 29 grams of infundibular myocardium.

Microscopic examination revealed cardiac valvular tissue which appeared to be normal except for small areas of myxomatous degeneration.

The postoperative course of the patient was uneventful. He was discharged from the hospital 7 days after operation and he has had no difficulties since then.

Discussion

This unusual case had all the clinical and hemodynamic findings associated with valvular and infundibular pulmonary stenosis. The surgical observation of a normal pulmonary valve initially proved to be disconcerting to the cardiologist until further observation disclosed the true nature of the obstruction. To our knowledge this anomaly in an otherwise normal heart has not been described in the literature.

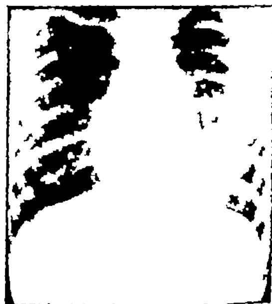


Fig. 2. Posteroanterior roentgenogram of the chest. The heart is slightly enlarged, the pulmonary artery segment full, and the lung vasculature diminished.

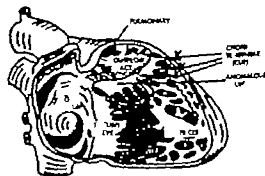


Fig. 3. Artist's interpretation of anomalous tricuspid valve in pulmonary outflow tract.

Ehrenhaft[1] excised an anomalous tricuspid leaflet which was attached to the papillary muscles by chordae tendineae but which was unattached at the base so that the free floating leaflet produced obstruction at the pulmonary outflow area The present case differed considerably from Ehrenhaft s case since this was a complete valve with two leaflets and was attached to the infundibular area as if at an annulus

Recently Levy and associates have presented 3 cases of corrected transposition of the great vessels in which accessory valvular tissue produced a subpulmonary stenosis and McLean[3] has reported a case of subaortic stenosis due to reduplication of the mitral valve leaflets

Summary

A case of obstruction of pulmonary tract outflow due to reduplication of the tricuspid valve in the right ventricular outflow tract has been presented Surgical excision of this structure was successful

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Atrial dissociation

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The electrocardiographic demonstration of atrial dissociation has been reported only rarely in man The purpose of this paper is to present electrocardiograms which clearly show atrial dissociation with two distinct sets of P waves which subsequently fused to form a single P wave

The previously reported cases of atrial dissociation were extensively reviewed by Deitz and associates[1] in 1957 Subsequent cases have been reported by others [6]

Various symbols have been used to designate the two sets of atrial waves in previous publications [1-6] The notations *P* and *p* are used in this paper to designate the primary and secondary atrial waves respectively

Case report

A 75 year-old retired Negro construction worker was admitted to the hospital with symptoms of progressive congestive heart failure of one month's duration Physical findings on admission included cervical venous distention cardiomegaly proto diastolic gallop rhythm bilateral moist pulmonary rales hepatomegaly and pedal edema The admission electrocardiogram (Fig 1) revealed rhythmic deflections best seen in Lead II III and aV_F which did not seem to be related to the remainder of the P QRS T complex The nature of these deflections was not clear Long strips of Lead II (Fig 2) revealed them to be the p waves of atrial dissociation The rate of the waves I was was 130 per minute The secondary p waves occurred at a rate of 75 per minute

The patient was treated with oxygen morphine aminophylline meralluride and digoxin An electrocardiogram taken 7 hours after admission (Fig 3) showed that the P and p waves had fused The patient did not respond to therapy and died 16 hours after admission Permission for autopsy was not granted

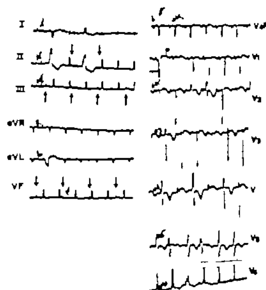


Fig 1 The initial electrocardiogram revealed rhythmic deflections (*indicated by arrows*) which were best seen in Leads II III and aV The origin of these was not clear but they did not seem to be related to the remainder of the P QRS-T complex Fig 2 demonstrates their nature more clearly (Time 3 P M)

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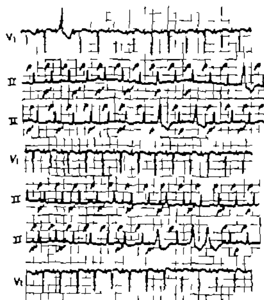


Fig 2 The lead selector was alternated between Leads II and V T o distinct sets of atrial wa es ar seen The rate of the P wa is 130 per minute and they are uniformly conducted to the ventricle The rate of the p wa es is 75 per minute and they bear no constant relationship to the other components of the electrocardiogram (Time 3 P M)

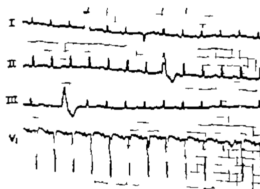


Fig 3 Seven hour later the P wave and the p wa have fused to form a single not hed P ave (Time 10 P M)

Discussion

*Atrial dissociation has been found in var*ious clinical conditions including chronic glomerulonephritis rheumatic heart disease arteriosclerotic heart disease digitalis intoxication and goiter and in normal children according to a review of previously reported cases by Arbarquez and LaDue[4]

The p wave probably originates in a constantly active focus somewhere in the atria which is capable of depolarizing only the immediately surrounding area It should be noted that in no instance did the atrial activity designated *p* seem to be conducted to the ventricle *This obser*vation has been made previously by others[1 6] This would imply that this portion of the atrium is electrically isolated The mechanism by which the isolation is brought about is unknown but its temporary nature is indicated by the merger of the P and p waves in Fig 3 to form a single notched P wave The notching is probably due to some degree of remaining intra atrial block

Summary

An *electrocardiographic demonstration* of atrial dissociation is presented

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Clinical pathologic conference

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Clinical abstract

DR RAGHIB This 13 year-old girl had been delivered spontaneously following a normal pregnancy The weight at birth was 8 pound and 3 ounces Although the neonatal period was reported to have been uneventful roentgenoscopy had been done and roentgenograms made when the patient was only a few weeks old These were reported to have shown an unusual cardiac shadow No murmur was detected at that time Except for the usual childhood diseases the patient remained asymptomatic until the age of 7 years when she was examined for an infection of the upper respiratory tract At this time a cardiac murmur was recorded for the first time and the patient was hospitalized elsewhere with the diagnosis of possible rheumatic fever During this hospitalization the patient was digitalized and received antibiotics In 1958 when the patient was 8 years old cardiac catheterization was done to *exclude the possibility of congenital heart disease* The results of this study were not considered to be significant and the patient was continued on a program of restricted activity and prophylaxis against rheumatic fever Gradually she developed a feeling of fatigue and this was followed by overt exercise intolerance In 1962 because of progressive symptoms the patient was seen at another cardiac center and underwent catheterization of the right and left sides of the heart After these studies all medications were discontinued Later at the age of 13 years the patient was referred to the University of Minnesota Hospitals for consideration for operation A few weeks prior to admission the patient had complained of episodes of thoracic pain which were not related to any activity Episodes of dizziness and probable *syncope occurred*

Physical examination showed the patient to be normally developed and noncyanotic The respiratory characteristics were normal the rate was 20 per minute The pulse was regular and the beats numbered 90 per minute

The brachial blood pressure was 115 mm Hg systolic and 63 mm Hg diastolic The femoral pulses were of good amplitude

Examination of the heart revealed an active precordium but no thrill The apical beat was felt in the fifth left intercostal space beyond the midclavicular line A Grade 3 moderately rough systolic ejection murmur was heard loudest at the left sternal border in the third left intercostal space The murmur was transmitted slightly toward the cardiac apex Neither a diastolic murmur nor a click was heard At the pulmonary area the second cardiac sound was normally split

The liver and spleen were not enlarged There *was no edema*

The results of the usual laboratory studies were not abnormal A skin test using mumps virus antigen gave a questionably positive reaction at 22 hours but was negative at 43 hours

DR ADAMS The statement that an unusual cardiac shadow was noted by radiologic examination when the patient was a young infant does not suggest any specific condition The history reveals that a murmur was first heard at the age of 7 years Acquired cardiac disease secondary to rheumatic fever cannot be excluded with certainty

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Because of the noncontributory results of a catheterization of the right side of the heart done in 1958 we should be able to eliminate those lesions which cause (1) severe pulmonary venous obstruction (2) intrapulmonary arterial obstruction (3) pulmonary valvular stenosis and (4) defects allowing left to right shunt. As a result of these eliminations our attention becomes focused upon those lesions which involve the left ventricle or the aorta.

Episodes of thoracic pain may be related to severe right ventricular hypertension but for the reasons mentioned this phenomenon must be discounted. On the basis of the information thus far valvular supravalvular or subvalvular aortic stenosis must remain the foremost diagnostic probabilities. Idiopathic cardiac hypertrophy and endocardial sclerosis of the late appearing variety should also be kept in mind.

In my experience aortic valvular stenosis causes murmurs which may be heard during the first few days of life. In contrast to this murmurs associated with shunts frequently appear later. The absence of (1) a thrill in the suprasternal notch (2) of an ejection murmur in the aortic area and (3) of an early systolic click would each be a factor against the diagnosis of acquired or congenital aortic valvular stenosis.

A history that multiple members of the family had died of cardiac disease would focus suspicion on the possibility of the familial variety of subaortic stenosis. A description of unusual facies or of mental retardation would suggest familial supravalvular aortic stenosis. Am I correct in assuming that if present such features of history and physical examination would have been stated?

DR RAGHIB No such history was present.

DR ADAMS Endocardial sclerosis with or without obstruction of the left ventricular outflow tract is usually diagnosed in early life because of the early onset of symptoms and the peculiar clinical picture. When symptomatic idiopathic cardiac hypertrophy secondary to endocardial sclerosis occurs later in life as reported by Lynfield and co-workers of Gasul's group the patients invariably manifest pulmonary hypertension. Anomalous origin of the left coronary artery from the pulmonary trunk has been recognized as causing symptoms under circumstances similar to those described here. Thus one is led to conclude that idiopathic cardiac hypertrophy of nonfamilial type anomalous origin of the left coronary artery from the pulmonary trunk and acquired cardiac disease are the diagnoses with the highest levels of possibility. Dr Raghib do you have the electrocardiographic findings?

DR RAGHIB The electrocardiogram showed sinus rhythm with a rate of about 90 cycles per minute. Left axis deviation of −20 degrees (Fig 1) was present. There

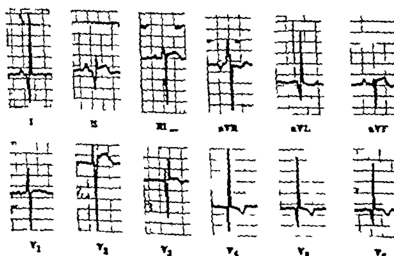


Fig 1 The electrocardiogram. Leads V4–V6 were recorded at half standard.

were high voltage QRS complexes in the left precordial leads indicating left ventricular hypertrophy. The isodiphasic QRS complexes in Lead V_1 may suggest right ventricular hypertrophy additionally. The deep and wide Q waves in Leads I, II, aVL, V_4, V_5 and V_6 with negative T waves in the left precordial leads and the elevated S-T segment in Lead II favor a diagnosis of diffuse myocardial damage of the anterolateral wall.

*Table I Data from catheterization of the right side of the heart obtained in 1958 when the patient was 8 years old**

Site	Pressure (mm Hg)	O_2 saturation (per cent)
Superior vena cava		75 1
Right atrium	(M 4)	66 7
Right pulmonary artery (wedge)	(M 13) v = 16	99 8
Right pulmonary artery	20/15 (M 17)	60
Right ventricle (infundibulum)	30/0/3	57
Right ventricle (apex)	30/0/5	58 6
Brachial artery	92/40	91
		93
		98

* V [illegible] M = Mean pressure

*Table II Summary of data from catheterizations of the left and right sides of the heart obtained in 1963 at the University of Minnesota Hospitals when the patient was 13 years old**

Site	Pressure (mm Hg)
Right atrium	a = 7, v = 4 (M 5)
Left atrium	a = 16, v = 22 (M 14)
Left pulmonary vein (wedge)	27/13 (M 20)
Left ventricle (apex)	180/0/20
Left ventricle (outflow tract)	100/0/20
Aorta	100/50 (M 65)
Right ventricle (apex)	60/0/5

*These [illegible] comparable with the results obtained in 196[illegible]. In the study of 196[illegible] the pulmonary arterial pressure was 30/16 mm Hg and the right ventricular pressure was 60/0 mm Hg. No [illegible] de[illegible] for [illegible] but it was obtained in the study. M = Mean pressure

DR ADAMS This type of electrocardiogram may be seen in several conditions; these include myocardial infarction, marked myocardial hypertrophy, glycogen storage disease, severe aortic stenosis, endocardial sclerosis and anomalous origin of the left coronary artery from the pulmonary trunk.

Although cases of glycogen storage disease may yield an electrocardiographic pattern like the one illustrated, that condition may show features which are somewhat different from this electrocardiogram. In glycogen storage disease the cardiac rate tends to be more rapid, the P-R interval shorter and the QRS interval wider than that shown here. Also, the abnormalities of the P-R and QRS intervals may be such as to make the two respective intervals of nearly equal length.

Myocardial infarction as a consequence of occlusive coronary artery disease may occur rarely in children, but in such cases episodes of angina pectoris or of myocardial infarction are more specific than are the findings in this case.

At this point, by the electrocardiogram alone, we cannot exclude endocardial sclerosis, anomalous origin of a coronary artery from the pulmonary trunk, diffuse myocardial hypertrophy or severe aortic stenosis.

DR RAGHIB Before the roentgenograms and angiocardiograms are shown, I shall ask Dr Wang to present the data obtained from cardiac catheterization.

DR WANG Three studies had been done, two elsewhere when the patient was 8 and 12 years old and the third at our institution when she was 13 years old.

The study at the age of 8 years was a catheterization of the right side of the heart done while the patient was sedated. Except for borderline elevation of the pulmonary arterial wedge pressure, the results were considered to be normal (Table I).

The second and third studies consisted of catheterizations of the left and right sides of the heart and angiocardiography. Comparable results were obtained from these two series of studies. These indicated the presence of a marked systolic pressure gradient between the left ventricular cavity near the apex and the aorta and a moderate systolic pressure gradient between the right ventricular cavity and the pulmonary

trunk (Table II) There was no systolic pressure gradient across either the aortic or the pulmonary valves The pull back tracing from the apex of the left ventricle to the aorta showed a significant decrease in the systolic pressure at the mid portion of the ventricular cavity below the expected location of the subaortic region

The mean left atrial pressure obtained by transseptal puncture was within normal limits indicating the absence of left ventricular failure

The recordings of the peripheral arterial pressure pulses showed that the pulse of the beat which followed an extrasystole was less than the amplitude of the regular beats a phenomenon observed by Brockenbrough and associates[3] in the muscular type of subaortic stenosis

The finding of muscular subaortic stenosis in association with right ventricular infundibular obstruction suggests a diffuse type of myocardial hypertrophy

DR RAGHIB Dr Amplatz would you please comment on the roentgenographic and angiocardiographic findings

DR AMPLATZ The posteroanterior view of the thorax (Fig 2,a) shows severe cardiomegaly and essentially normal pulmonary vasculature In the lateral view (Fig 2 b) there seems to be right and left ventricular hypertrophy and probably some degree of left atrial enlargement The ascending aorta is not prominent

The selective left ventriculogram (Fig 3 a and b) demonstrates an enlarged ventricular cavity which is heavily trabeculated The striking finding is marked diffuse thickening of the left ventricular wall and of the ventricular septum This causes a filling defect near the mitral valve suggestive of a tumor mass There is also a question whether this mass of muscle is interfering with the function of the mitral valve During systole the left ventricular outflow tract seems to be very narrow but during diastole it appears to be of adequate width

The aortogram (Fig 3 c) shows minimal regurgitation into the left ventricle but the aortic valve appears to be anatomically normal The left atriogram (Fig 3,d) made by transatrial septal puncture shows a normal sized left atrium and no gross abnormalities of the mitral valve The angiocardiographic findings are consistent with diffuse muscular hypertrophy which may be causing some subaortic obstruction

DR RAGHIB With the diagnosis of diffuse myocardial hypertrophy and subaortic stenosis the patient was referred to the surgical staff for treatment Dr Lillehei would you please describe the operative procedure

DR LILLEHEI The preoperative diagnosis was diffuse myocardial hypertrophy with subaortic stenosis It was thought that excision of some of the subaortic muscular mass might decrease the heavy work of the left ventricle

With the patient supported by extra



Fig Roentgenogram of the thorax when the patient was 13 years old a Posteroanterior view b Lateral view

corporeal circulation and oxygenation, the left atrial cavity was exposed by way of the interatrial groove. The anterior leaflet of the mitral valve was incised along its annular attachment to expose the subaortic area of the left ventricle. Pieces of myocardial and endocardial tissue were removed from the ventricular septum in order to alleviate the subaortic stenosis. By palpation the aortic cusps appeared to be normal. To conclude the procedure, the incisions in the mitral valve and atrial groove were closed in the usual way, and the operation was terminated successfully.

About one hour after the operation the patient developed pulmonary edema and became cyanotic. Tracheotomy was performed. Determination of the blood volume revealed a value of 90 c.c. of blood per kilogram of body weight. The venous pressure was elevated, measuring 24 cm. of water. Two hours after operation the patient developed cardiac arrest. Bedside venesection of 200 c.c. of whole blood was done, cardiac stimulants were used, and external cardiac massage was performed. The cardiac action was restored, but about 3 hours later cardiac arrest recurred and

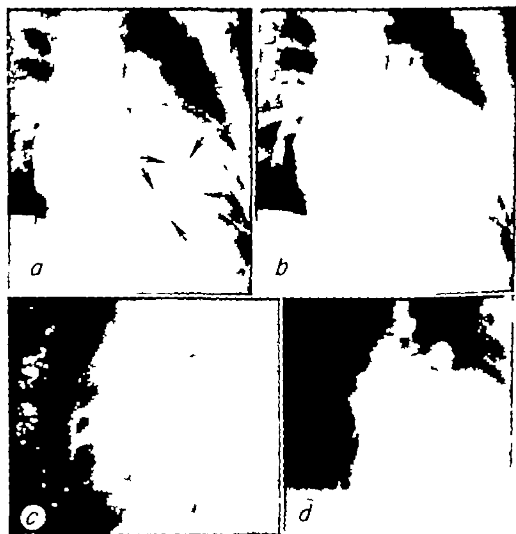


Fig. 3, a and b, Left ventriculogram made by transthoracic puncture of the left ventricle. a, Systole. Marked thickening of the left ventricular wall and large filling defect (arrows) near the mitral valve. b, Diastole. c, The aortogram. The aorta was entered through the left ventricle. Normal aorta and minimal regurgitation into the left ventricle. d, Left atriogram made by transatrial septal puncture. The tip of the catheter is in the left atrium near its lateral wall. Normal left atrium and mitral valve. Partial filling of left ventricle.

this time the efforts for resuscitation were in vain.

DR. RAGHIB: Dr. Edwards, would you please describe the pathologic findings.

DR. EDWARDS: The heart was massively enlarged, weighing 850 grams. The enlargement consisted of extensive hypertrophy of the ventricular walls and of the ventricular septum. The thickness of the left ventricle measured 3.4 cm., that of the right ventricle 2.0 cm. (Fig. 4, *a* and *b*).

In the subaortic area of the left ventricle there was a raw area which corresponded to the site from which tissue had been excised at operation.

The massive hypertrophy of the ventricular septum was associated with distortion and apparent obstruction of the right ventricular infundibulum. The ventricular septum also bulged against the septal leaflet of the tricuspid valve.

No septal defects were present and each valve was intrinsically normal, as were the coronary arteries.

Histologic examination of the myocardium revealed hypertrophy of the fibers.

In the left ventricle multiple microscopic sized scars (Fig. 4, *c*) were present in addition to a small amount of excess connective tissue around the individual muscle fibers. The latter feature was more prominent in the right ventricle, where scarring was rare (Fig. 4, *d*).

This case differs from the usual example of subaortic stenosis. It appears primarily to represent extreme diffuse myocardial hypertrophy, with subaortic and right ventricular infundibular stenosis being secondary consequences. Dr. Raghib, you have reviewed some of the literature on this type of problem. Perhaps you would care to summarize it.

DR. RAGHIB: Several names, such as "familial cardiomyopathy," "cardiac hypertrophy and insufficiency," "hereditary cardiovascular dysplasia," "obstructive cardiomyopathy," "asymmetrical hypertrophy," and "idiopathic myocardial hypertrophy," have been used in reference to cases of this type.

In the literature there are reports of several cases of idiopathic myocardial hypertrophy which involved the heart diffusely. Some cases showed a familial trend which extended over several generations, and in some cases no familial tendency was demonstrable. Thus, one might conclude that there may be familial[6] and nonfamilial[7-11] forms of idiopathic myocardial hypertrophy.

In the reported cases of the familial form the disease most commonly became apparent when the patients were in the second or third decades of life. In such cases it was possible, as in this case, that the patients had had the disease since birth but had remained asymptomatic until adulthood. In reported instances of the familial form the clinical picture varied from sudden death without a history of cardiac disease to a state of protracted cardiac failure. According to the literature, a few patients lived to be older than 50 years of age before idiopathic myocardial hypertrophy was diagnosed, yet some died in infancy. At necropsy, cardiomegaly, including left ventricular hypertrophy, was universal, and histologic findings of myocardial hypertrophy with localized areas of scarring of various degrees were described in all patients, regardless of the clinical picture and regardless of the age at death.

Similar clinical and pathologic findings have been described in reported cases of the nonfamilial form of idiopathic myocardial hypertrophy.[11, 1] Thus, one is led to suspect that both in the familial and in the nonfamilial forms the etiological factors may be the same.

There are also reports of localized, so-called asymmetrical hypertrophy[7] of the myocardium. In these cases the clinical picture was the same as in the diffuse forms of idiopathic myocardial hypertrophy. The histologic findings in the cases of asymmetrical hypertrophy differed from the findings in diffuse hypertrophy by showing a bizarre arrangement of hypertrophied muscle fibers with excess loose connective tissue around each individual muscle fiber in the involved areas.

This histologic difference may suggest different etiological factors for the cases of asymmetrical hypertrophy of the myocardium.

Paré[4] and associates examined 77 members of a family with idiopathic myocardial hypertrophy. Finding 20 cases in persons of varying ages in this group, they concluded that the myocardial hypertrophy

in this family was a nonsex-linked Mendelian dominant trait. Similar conclusions were suggested by Whitfield and associates[3] and by Hollman and associates[4] after their respective studies.

In 3 of the 20 cases of Hurd,[1] histologic examination of the myocardium was done. In 2, the same histologic characteristics were present as those described for the asymmetrical form. This leads one to suspect that the cases of asymmetrical hypertrophy may perhaps represent early or minor manifestation of diffuse idiopathic hypertrophy, the condition in the case presented in this conference.

In this description of Pare's 2 cases with

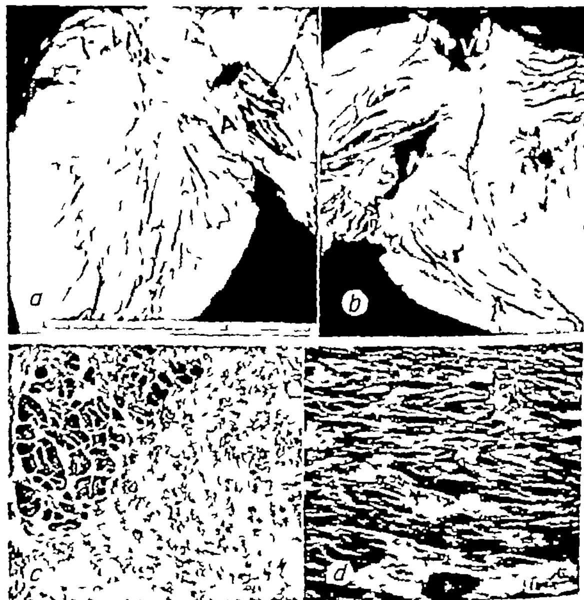


Fig. 4. Left ventricle and aortic valve. Hypertrophied left ventricular wall. The break at the base of anterior mitral leaflet (AM) is an artifact and represents the surgical incision to the left ventricular outflow tract through the left atrium. Beneath the aortic valve the rough area on the ventricular septum is the site of surgical excision of tissue. b, The interior of the right ventricle. Beneath the pulmonary valve (PV) the infundibulum is narrowed by the prominently hypertrophied ventricular septum. c, Photomicrograph of myocardium of left ventricle. Large area of fibrosis and hypertrophied muscle fibers. (Hematoxylin and eosin. ×110.) d, Right ventricle. Hypertrophied muscle fibers. Minimal fibrous tissue around individual muscle fibers. (Hematoxylin and eosin. ×110.)

histologic findings of a bizarre arrangement of hypertrophied myocardial fibers it is of interest that in addition to diffuse hypertrophy of the myocardium there was mention of a peculiar nodular mass in the cephalic two thirds of the interventricular septum

Findings of a peculiar nodular mass in the ventricular septum and of a bizarre arrangement of hypertrophied myocardial fibers led some authors[1,7] to suggest that there is a defect in the embryological development of the cardiovascular system in idiopathic myocardial hypertrophy Brachfeld and Gorlin[8] in primarily considering muscular subaortic stenosis suggested that arrest of the embryonic maturation of the bulbus cordis while it is still a contractile muscular structure could cause obstruction of the outflow tract of the left ventricle by premature contraction during systole Thus they conclude that in subaortic stenosis muscle dysfunction is the primary factor and left ventricular hypertrophy is a secondary factor Left ventricular hypertrophy will add an obstructive component to primary subaortic obstruction

Assumed arrest of maturation of the bulbus cordis perhaps explains isolated cases of cardiac hypertrophy with subaortic stenosis In the familial form of cardiac hypertrophy some genetic factors rather than pure mechanical ones may be involved Genetic factors may affect either maturation of the bulbus cordis or the hemodynamics and the metabolism of the myocardium Answers to these questions will require extensive experimentation

Whalen and associates[1] reported on a patient who showed clinical genetic and laboratory features of idiopathic myocardial hypertrophy without a significant systolic gradient between the left ventricular cavity and its outflow tract during rest After infusion of isoproterenol or during exercise a marked systolic gradient developed between the left ventricular cavity and its outflow tract

These investigators administered isoproterenol to 15 other patients with left ventricular hypertrophy of various causes In none of these did they observe a pressure gradient between the main part of the left ventricle and its outflow tract They concluded that in these 15 subjects the hypertrophy was functionally different than in cases of idiopathic myocardial hypertrophy

Krasnow and associates[9] infused isoproterenol into 8 normal dogs and followed the immediate effects In 2 of 8 animals a differential in pressure was demonstrated across the left ventricular outflow tract

Recently Kobernick and associates[10] determined the qualitative activity of various cardiac enzymes in a case of idiopathic myocardial hypertrophy and in 6 control specimens with or without cardiac hypertrophy from other causes These studies showed decreased levels of succinic dehydrogenase activity in the case of idiopathic myocardial hypertrophy whereas the activities of other enzymes were at the same levels as in the control cases

Before the arrest of maturation of the bulbus cordis is accepted as the sole etiological factor in this condition further research on hemodynamic and metabolic aspects of the myocardium is necessary

It seems likely that in idiopathic myocardial hypertrophy the obstruction of the outflow tracts of both ventricles is the result of diffuse hypertrophy of the myocardium as in this case of which the etiology may be either hemodynamic or metabolic For each of these there may be a genetic stimulus

Diagnosis Idiopathic myocardial hypertrophy with severe subaortic stenosis and moderate obstruction of right ventricular infundibulum

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Atrial septal defect

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Atrial septal defect is one of the most common forms of congenital heart disease found in youths and adults[1] and was encountered in 245 of 1,439 patients with congenital heart disease seen by one of us (V.S.) in this Clinic.[2] The physical signs are so characteristic that a precise diagnosis can usually be made at the bedside. Electrocardiographic, phonocardiographic, and radiologic examination provides accurate confirmation, so that cardiac catheterization is often not essential.

With the development of hypothermic and cardiac bypass procedures these defects are now amenable to surgical correction. However, it is well to have some idea of the natural history of the disease, the anatomic variants and complications, the abnormal hemodynamics produced by these defects, and the influence of the latter on the clinical findings.

Embryology

Many of the embryologic details responsible for this malformation have been well established, whereas others are still speculative and require further study. Briefly, the endocardial cushions evolve from the middle of the tube-like primitive heart, dividing it into two chambers, one of which is destined to be atrial and the other ventricular. The cushions themselves contribute to the formation of the atrioventricular valves and the septa.[3] The septum primum grows downward from the dorsal and cephalic walls of the atrium and the space between it and the endocardial cushions is known as the *ostium primum*. This opening is sealed as the septum primum continues to grow and fuses with the endocardial cushions. Communication between the two atria is maintained through the *ostium secundum*, which is formed when part of the wall of the septum primum disappears. Downward growth of the septum secundum covers the foramen primum but leaves an oblique opening—the foramen secundum—through which the flow of blood from the right to the left atrium is maintained. The right atrium is formed by incorporation of part of the right sinus venosus, the inferior vena cava, and the superior vena cava into the primitive right atrium, and similarly, the left atrium is formed by incorporation of part of the pulmonary veins into the left atrium.

Normally, the septum primum and septum secundum fuse after birth, completely separating the two atria. In 12 to 25 per cent of healthy subjects the two septa are not united, but are functionally closed since left atrial pressure exceeds right atrial pressure, forcing the two septa together. Reversal of the normal pressure gradient separates the septa and results in a right-to-left shunt through the opening. Deficiency of the septum primum or the

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the development of pulmonary hypertension,[12] usually with atrial fibrillation. But before this is accepted, left ventricular failure, e.g. that due to hypertension, mitral valve disease, thyrotoxicosis, etc., must be excluded.[12] Since both atria are in free communication, failure of the left side can be detected early by the elevation of the systemic venous pressure.

When malformation of the mitral valve, acquired or congenital, is present, the effects of mitral stenosis or incompetence are superimposed on the changes produced by the atrial septal defect. Because the left and right atria are in free communication, the pressure effects are dissipated through both atria, which perhaps accounts for the slightly elevated right atrial pressure and the absence of back pressure on the pulmonary capillaries. Should the tricuspid valve be involved, the effects of tricuspid incompetence are superimposed on the other hemodynamic disturbance present.

When a ventricular septal defect coexists, the hemodynamic changes do not differ from those produced by an ordinary uncomplicated ventricular septal defect except that blood may be shunted directly from the left ventricle into the right or left atrium, or from the left ventricle into the right ventricle and the right atrium because of associated valve deformities. The effects of the ventricular septal defect depend on its size and the pulmonary vascular resistance.

Clinical findings

Characteristic of secundum and sinus venosus defects is the higher incidence in females (3:2), the rare discovery in infancy, the *mild* or absent symptoms in the first three decades of life, and the increasing disability in the third and fourth decades of life due to the late development of heart failure and severe pulmonary hypertension.[13,14] Most patients are referred because of murmurs *noted* during routine physical examination for some unrelated illness or during *routine medical* examination at school, during pregnancy or for life assurance. Often the abnormality is first noted during *mass radiography* or after radiologic examination for pulmonary infection. Even when attention has been drawn to the heart, especially in subjects under 30 years of age, the patient often will not admit to symptoms. When symptoms are present they usually do not amount to much more than mild effort dyspnea, fatigue or palpitations, although a background of respiratory infections, especially during childhood, is not uncommon. Often supposedly symptom free patients appreciate their preoperative limitations only after the defect has been closed surgically.

Most patients are aware of their disease by the third decade of life, although occasionally the condition is discovered for the first time in the sixth or seventh decade or later.[19,20] Because of the relatively benign, well tolerated nature of the condition, it is compatible with a full, normal asymptomatic lifespan. Failure to appreciate this leads to frequent errors in diagnosis in persons beyond middle age and in the elderly. A familial occurrence is also well documented but is uncommon.[1] These defects are approximately four times as common as endocardial cushion defects.

Characteristic of endocardial cushion defects, on the other hand, is the equal sex incidence, the common discovery in infants, the severity of the symptoms, the frequent finding of severe pulmonary hypertension and the increasing disability, so that the condition is recognized at a far earlier age and survival to adulthood is less frequent.[4,6,7] Exertional dyspnea, fatigue, troublesome palpitations and recurrent respiratory infections are more prominent, and congestive cardiac failure is not rare. Because the murmurs are much more prominent, attention is drawn to the heart at an earlier age than in patients with secundum defects.

Physical examination

Body development and stature are normal in most patients with secundum or sinus venosus defects, although arachnodactyly, a high arched palate and a gracile habitus have been noted.[9] Other congenital stigmata are generally absent. Poor bodily growth and retardation of development tend to be more common in patients with endocardial cushion defect, especially when the complete variety is present. Septal defects are common in

Mongolism the complete variety of endocardial cushion defect is the most frequent association [1,39]

The jugular venous pressure and pulsations are normal except in the presence of cardiac failure. The peripheral pulse and blood pressure are normal. Atrial septal defect is the one congenital heart condition in which atrial fibrillation occurs with any degree of frequency. This is probably related to the age of the patient since it rarely occurs before the fourth decade. When present, especially at an early age, associated mitral valve disease (Lutembacher's syndrome)[40] should always be suspected.

Palpation of the chest is very important. Clear evidence of diastolic overload of the right ventricle is usually present. The forceful, often heaving type of apex can be mistaken for an overactive left ventricle. The apex, however, is formed by the enlarged right ventricle, which can readily be recognized by the parasternal lift which is continuous with the apical thrust. Pulsation over the outflow tract and pulmonary artery is frequently visible and palpable and an accompanying thrill is not rare, especially when the chest wall is thin and a left parasternal bulge is present, deforming the thoracic cage. When atrial septal defect is complicated by gross mitral incompetence or a ventricular septal defect, the apex is left ventricular in type and a low parasternal thrill may be present.

Auscultation

A pulmonary ejection systolic murmur is nearly always present, usually Grade 2-3/6 in intensity, differing in no way from the innocent pulmonary systolic murmur of youth and childhood. Occasionally it is very loud (Grade 5/6) and associated with a thrill which usually but not necessarily is due to a gradient across the pulmonary valve. It is well heard in the back below the scapulae, presumably because of downward conduction through the pulmonary arteries. One of the most important diagnostic findings is a diastolic murmur in the tricuspid area, often with a distinctive high pitch and varying remarkably with respiration; in fact, it sometimes becomes audible only at the height of inspiration. At times this murmur is loud and widespread, radiating to the apex. Since the apex and the whole front of the heart is formed by the right ventricle, the murmur may be mistakenly attributed to mitral stenosis. The murmur is caused by the increased flow across normal tricuspid valves. When the murmur is soft and high pitched, differentiation of it from the murmur of pulmonary incompetence may be difficult because both murmurs commence at nearly the same phase of diastole; the pulmonary diastolic murmur is delayed because of prolongation of right ventricular systole, and the tricuspid valve opens early because of increased atrial filling. Pulmonary incompetence can only be diagnosed with certainty when the murmur is localized to the pulmonary area or when severe pulmonary hypertension is present.

A pansystolic murmur at the apex indicates the presence of mitral incompetence and is often accompanied by an apical mid-diastolic murmur. In endocardial cushion defect the murmur tends to radiate medially rather than laterally.[11,37] In fact, it may be mistaken for the murmur of a ventricular septal defect radiating toward the apex. The peculiar situation of the valve deformity results in an anteromedially directed jet. Thus *a loud systolic murmur at the tricuspid area, often with a thrill, may be due to mitral incompetence, tricuspid incompetence, or a ventricular septal defect.*

Abnormal splitting of the second sound is one of the most striking physical signs in atrial septal defect.[17] The width of splitting is not the feature, since splitting is most commonly not more than 0.04 second in held expiration, but fixity of the split to the ear is characteristic. Normally, the second sound closes completely on expiration and widens to a variable extent on inspiration, and it is the change from a split to a single sound that can be readily appreciated. Although phonocardiographically some change in the degree of splitting is often present, it is extremely difficult at the bedside to appreciate movement of the second sound when the sound is never single or narrowly split. It is likewise very difficult to appreciate movement of the widely split

second sound of pulmonary stenosis or ventricular septal defect The pulmonary component of the second sound is usually of normal intensity except in the presence of pulmonary hypertension When severe pulmonary hypertension is present e g in Eisenmenger's syndrome wide splitting of the second sound is said to indicate atrial septal defect[20] We have been deceived by this sign in 2 patients with reversed patent ductus and in cases of proved atrial septal defect we have found single second sounds

An early systolic ejection sound or click[21] usually indicates pulmonary hypertension or marked pulmonary arterial dilatation Wide splitting of the first sound with accentuation of the tricuspid component presumably due to overdistention of the right ventricle with delayed closure of the tricuspid valve is commonly encountered Confusion with the pulmonary ejection sound can readily occur The loud first sound may raise a suspicion of mitral stenosis

In our experience with approximately 300 patients who had an atrial septal defect we found four fairly clearly defined clinical patterns (1) *Classic atrial septal defect* The majority of secundum and sinus venosus defects and approximately 25 per cent of endocardial cushion defects fall into this group The signs are those of increased flow across the pulmonary and tricuspid valves without evidence of atrioventricular valve disease or ventricular septal defect (2) *Atrial septal defect with mitral incompetence* Approximately half our patients with endocardial cushion defects presented signs of mitral incompetence in addition to those of increased flow across the pulmonary and tricuspid valves Rarely does rheumatic or even congenital mitral incompetence complicate secundum defects (3) *Ventricular septal defect with or without mitral incompetence* This occurred in approximately 25 per cent of our cases of endocardial cushion defects and in cases of secundum defects associated with independent ventricular septal defects The clinical signs are dominated by a systolic murmur often with a thrill at the fourth left intercostal space whether a ventricular septal defect is in fact present or not Pulmonary systolic murmurs splitting of the second sound and mitral murmurs occur so frequently in uncomplicated ventricular septal defects that in atrial septal defect may not even be suspected (4) *Eisenmenger's syndrome*

Phonocardiography

Typical phonocardiograms of secundum and primum atrial septal defects are shown in Fig 1 Pulmonary atrioventricular and ventricular septal defect murmurs have well known configurations by which they can usually be recognized The relatively fixed splitting of the second sound has been amply documented[20] and analyzed[26,27] Normally on inspiration the pulmonary component of the second sound (P) moves away from the aortic component (A) because of the increased right ventricular filling and prolongation of right ventricular systole associated with the increased systemic venous return to the heart On expiration P_2 moves in (right ventricular systole is shortened) and A moves out because of prolongation of left ventricular systole associated with the increased pulmonary venous return Splitting on inspiration is followed by superimposition of A and P_2 on expiration In atrial septal defect the two atria can be considered to be a common mixing chamber and flow into either ventricle is determined by the relative compliance of these two chambers The increased filling of the right atrium on inspiration is balanced by the diminished shunt from left to right atrium prolongation of right ventricular systole resulting in splitting of the second sound On expiration the increased filling of the right atrium from the left maintains right ventricular prolongation and persistence of the splitting

Electrocardiography

The P waves are usually of normal contour occasionally left or right or biatrial hypertrophy is present[33] The P R interval is usually normal but is more commonly prolonged in endocardial cushion defects than in secundum defects Right axis deviation with a mean QRS vector in the frontal plane between +90 and +150 degrees and a clockwise loop is characteristic of secundum and sinus venosus defects and is present in the majority of patients[13,14] On the other hand in the

majority of patients with endocardial cushion defects the mean QRS vector lies between −30 and −120 degrees (Fig. 2) with a counterclockwise loop.[16,43,44] These two distinctive patterns (Fig. 3) nearly always clearly separate the two conditions. It is more common, however, to find patients with secundum defects who have left axis deviation than to find patients with endocardial cushion defect who have a normal axis[4] (Fig. 3) or right axis deviation. In fact, the latter is highly exceptional.[47]

A typical rsR or rsR'S pattern in Lead V_1 (incomplete RBBB[17] or diastolic overload of the right ventricle[illegible]) is frequently present in both conditions. A tall R in Lead V_1 or an rR pattern suggestive of right ventricular hypertrophy or a qR or qRs pattern is not uncommon and, contrary to what has been reported by Davies and associates,[4] is not in our



Fig. 1. Phonocardiographic recordings from a patient with an uncomplicated secundum defect (*A*, *left*) and from a patient with an endocardial cushion defect (*B*, *right*) without a ventricular septal defect. Synchronous tracings from the carotid artery (*CAR*) and the jugular vein (*JUG*) are shown in *A*, and in both *A* and *B* the tracings are taken from the pulmonary area (*PA*), the tricuspid area (*4LS*), and the mitral area (*MA*). The *PA* and *4LS* tracings are recorded synchronously. At the pulmonary area in both *A* and *B* the pulmonary systolic murmur is ejection in type and is produced by increased flow across normal pulmonary valves. Wide splitting of the second sound (*2 2*) is present. At the tricuspid area in *A* the systolic murmur is ejection in type, radiating down from the pulmonary valves, and a tricuspid flow murmur (*DM*) associated with increased volume of blood flowing across normal tricuspid valves is recorded. The latter is well shown at the mitral area, where it may be mistaken for the murmur of mitral stenosis. At the tricuspid area in *B* the systolic murmur is pansystolic and of high frequency, so that it can readily be mistaken for the murmur of a ventricular septal defect. In fact, it is produced by the medial radiation of the mitral systolic murmur. The mid-diastolic murmur is probably due to fusion of a tricuspid flow murmur and an organic mitral diastolic murmur.

experience related to the pulmonary arterial pressure. Complete right bundle branch block, although frequently associated with pulmonary hypertension, occurs not uncommonly with relatively normal pulmonary arterial pressures and normal resistance. The additional finding of inverted T waves in Leads V_1–V_4 in adults was in our experience the only reliable electrocardiographic evidence of pulmonary hypertension. Small q waves in Leads V_6–V_7 occurred in more than a third of our patients and does not necessarily suggest an additional cause for left ventricular strain as suggested by Toscano Barboza and associates.[illegible]

Right axis deviation with a clockwise loop and a right ventricular diastolic overload or right ventricular hypertrophy pattern is not pathognomonic of secundum defects, since it occurs not infrequently in other forms of congenital heart disease such as pulmonary stenosis, as well as in acquired heart disease such as mitral valve disease and cor pulmonale. A similar tracing is occasionally encountered as in isolated congenital abnormality, sometimes associated with a pulmonary systolic murmur, a dilated pulmonary artery and wide splitting of the second heart sound.[illegible] In such a case cardiac catheterization is required in order to establish the diagnosis. However, when the clinical picture is that of an atrial septal defect, an electrocardiographic tracing of this kind is invaluable in differentiating secundum defect from endocardial cushion defect. On the other hand, left axis deviation with a counterclockwise loop and a diastolic overload or right ventricular hypertrophy pattern in an acyanotic patient is highly suggestive of defects in the region of the atrioventricular valves.[illegible] It is, however, encountered in uncomplicated ventricular septal defect (15 per cent of Toscano Barboza and Du Shane's 60 patients[illegible]).

Radiologic findings

The radiologic findings are frequently so characteristic that the diagnosis can often be made on screening or from the x-ray plates; in fact the condition is not infrequently discovered for the first time during this type of investigation. The heart is usually enlarged, with a cardiothoracic ratio above 50 per cent; this is due entirely to enlargement of the chambers of the right side of the heart and the main pulmonary artery. Generally, the larger the shunt, the greater the cardiothoracic ratio. Patients with endocardial cushion defects usually have even larger hearts, with an average cardiothoracic ratio of 60 per cent.[11] Left ventricular enlargement is difficult to assess in the presence of right ventricular enlargement because of displacement by the enlarged right ventricle. Left atrial enlargement is rare and, when noted, indicates involvement of the mitral valve.

The small aorta and large main and left pulmonary arteries (Fig. 4) produce a characteristic silhouette in the antero-posterior projection. The lung fields show the classic features of pulmonary plethora, with widely dilated pulmonary arteries proceeding well out to the periphery of the lung fields; the rounded shadows of these vessels can be seen end on. So characteristic is the appearance that, in a given patient with secundum atrial septal defect, the degree of left to right shunt can be fairly accurately assessed from a good

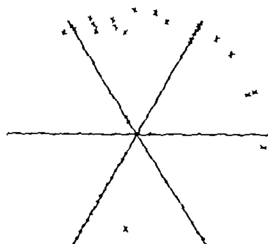


Fig. 2. The mean QRS vector in the frontal plane in 85 patients with surgically proved secundum defects and in 31 patients with surgically or necropsy proved endocardial cushion defects. In secundum defects the mean axis usually lies between +90 and +150 degrees; in endocardial cushion defect it lies between −40 and −170 degrees. Secundum defects with left axis deviation occur more commonly than endocardial cushion defects with normal axes.

posteroanterior film. Small shunts are characterized by the presence of plethora in the upper or mid zone, whereas large shunts are characterized by the presence of plethora throughout the lung fields.[11] Peripheral pruning, i.e., a sharp tapering off in caliber of the main pulmonary arteries, is seen in patients with a pulmonary systolic pressure above 60 mm. Hg. The striking feature of patients with severe pulmonary hypertension is the marked contrast between the enormously dilated main vessels near the hilum and the attenuated thread-like vessels and clear lung fields in the periphery. Hilar dance or marked pulsation of the pulmonary arteries on fluoroscopy is the hallmark of atrial septal defect; the excursions are greater in these patients than in those with any other left-to-right shunt. Radiology is of considerable value in determining the presence of a left-to-right shunt but does not differentiate a secundum from an endocardial cushion defect.

Anomalous pulmonary veins which enter the superior vena cava or the right atrium are difficult to see on plain films but can sometimes be clearly outlined by tomography.[1] Kerley B lines,[12] fine horizontal lines observed at the periphery in the basal regions and ascribed to pulmonary venous hypertension, are seen occasionally and usually indicate associated mitral stenosis.

Cardiac catheterization

Cardiac catheterization is most helpful in establishing the presence of an atrial septal defect, the size of the left-to-right shunt, the pulmonary vascular resistance, and the presence or absence of associated defects. Yet it often fails to differentiate a secundum from a primum defect. The following points, however, are worth remembering. A left-to-right shunt at the atrial level can always be detected in both conditions, but can, of course, also occur in the case of a ventricular septal defect with tricuspid incompetence and a left ventricular-right atrial communication. When the catheter is withdrawn directly from the left to the right ventricle (Fig. 5) without traversing an atrium, an endocardial cushion defect is present. A low crossing from right to left atrium, a further step-up in oxygen saturation from right atrium to right ventricle, and almost

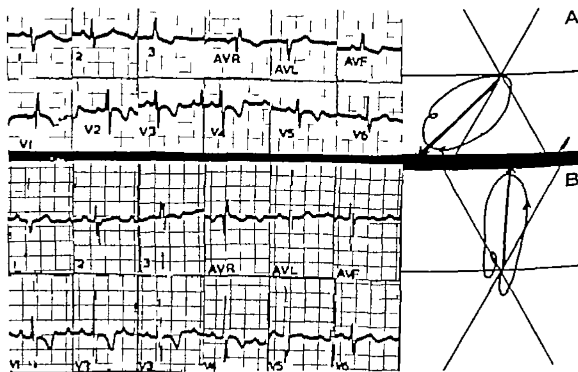


Fig. 3. Typical electrocardiograms found in cases of secundum defect (A) and of endocardial cushion defect (B).

identical dye-dilution curves from left and right pulmonary arteries favor endocardial cushion defects but are also found in cases of secundum defects Hemodynamic evidence of mitral incompetence is uncommon because the two atria form a large common chamber which dissipates the pulse waves and in any case secundum defects with mitral incompetence have the same effects as incompetent split mitral valves Differentiation of an endocardial cushion defect without a ventricular septal defect from one with a ventricular septal defect is even more difficult Left ventricular angiocardiography and intracardiac phonocardiography are the best techniques available for this Severe pulmonary hypertension and a significantly reduced arterial oxygen saturation usually favor the presence of a large ventricular septal defect

Sinus venosus defects and anomalous pulmonary venous drainage can usually be detected at catheterization The latter is best determined by the dye dilution technique since it is not always easy to be certain whether a catheter passed from the right atrium into a pulmonary vein has reached there directly or through an atrial septal defect

Common associations

1 Pulmonary valve gradient A loud pulmonary systolic murmur accompanied by a thrill in the pulmonary area is not a reliable indication that a gradient exists between the right ventricle and the pulmonary artery[18] We have found loud murmurs and thrills in patients with uncomplicated atrial septal defects without gradients and conversely gradients have been found when not clinically suspected Wide splitting of the second sound e g up to 0 07 second or more can occur without a gradient However when the phonocardiogram shows the pulmonary systolic murmur extending beyond A_2 we have always found a gradient In our experience the gradient has always been at valve level any infundibular gradient when present has always been trivial

Demonstration of a difference in systolic pressure does not necessarily indicate that true valvular stenosis is present[1] We found a gradient as high as 50 mm Hg with a right ventricular pressure of 80 mm Hg in a patient who had no narrowing of the pulmonary valve at the time of operation and in whom recatheterization



Fig 4 1 A a large left-to-right shunt with pulmonary arterial enlargement increased pulmonary arterial markings right atrial and right ventricular enlargement is present In B severe pulmonary hypertension is present The slight displacement of the heart to the left (commonly encountered in cases of atrial septal defect) exposes the markedly enlarged pruned right pulmonary artery The oligemic peripheral lung fields contrast sharply with the gross enlargement of the main pulmonary arteries

a year after repair of the defect showed normal right ventricular pressures and no gradient.[11] It is probable that the murmur and thrill in such patients is produced by a large flow through a valve ring which does not dilate to the same extent as do the pulmonary artery distally and the right ventricle proximally, thus resulting in an area of relative narrowing. It is our practice, therefore, to diagnose organic pulmonary valve stenosis only when a disproportionately large gradient is found with a small left to right shunt.

True organic pulmonary stenosis of varying severity undoubtedly exists. An extreme example is severe pulmonary stenosis with intact ventricular septum and reversed atrial shunt. Although the shunt is usually through a stretched foramen ovale, a true secundum defect may be present. Severe pulmonary stenosis alters the distensibility of the right ventricle so that resistance to filling may be only slightly less than, equal to, or exceed that of the left ventricle. As a result, a slight left to right shunt, no shunt, or a right to left shunt may be present, as occurs in Fallot's pentalogy.[14,15] Obstruction at the tricuspid valve or hypoplasia of the right ventricle produces similar effects on the shunt.

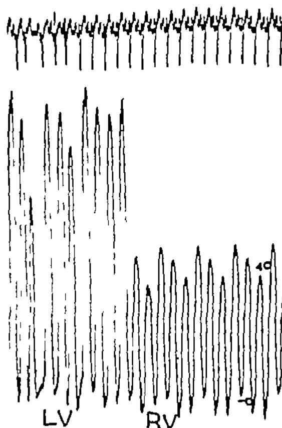


Fig. 5. Withdrawal of the catheter directly from the left to the right ventricle without traversing an atrium excludes secundum atrial septal defect but does not differentiate a complete from a partial endocardial cushion defect.

2. Pulmonary hypertension. When the pulmonary vascular resistance increases, the physical signs alter. As the signs of pulmonary hypertension begin to dominate the picture, the magnitude of the left to right shunt progressively diminishes. Thus the pulmonary and tricuspid murmurs are reduced or abolished, the second sound becomes loud, and splitting either persists, diminishes, or disappears. A pulmonary systolic ejection sound is nearly always present, and pulmonary incompetence is frequent. When a right to left shunt is established, cyanosis and clubbing result. Investigation by cardiac catheterization at this stage carries with it a significantly increased risk. Usually, the process takes a number of years to develop in the case of secundum defects, but occasionally, particularly after pregnancy, the course is more rapid. The ultimate clinical picture is that of Eisenmenger's syndrome.

Episodes suggestive of acute pulmonary arterial thrombosis frequently occur in the late stages of pulmonary hypertension, and massive thrombosis of the main branches can sometimes be recognized on the plain chest x-ray film.

In the complete variety of endocardial cushion defect with a large ventricular septal defect, the signs of severe pulmonary hypertension occur at a far earlier age, and severe disability in infancy is the general rule. The clinical picture is nearer that of a large ventricular septal defect than that of an atrial septal defect.

3. Eisenmenger's syndrome. Severe pulmonary hypertension with a reversed shunt at either the atrial, ventricular, or pulmonary arterial level characterizes Eisenmenger's syndrome.[16] The clinical pictures may be identical, whatever the

pathology. Atrial septal defect can be suspected by the persistence of splitting of the second heart sound, the disproportionate size of the pulmonary arteries and the presence of right bundle branch block. The diagnosis can be made with certainty only by catheterization and angiocardiography.

4. *Mitral valve disease.* Rheumatic mitral valve disease complicating secundum defects occurs in approximately 10 per cent of the cases;[11,15,18] congenital mitral valve disease is rare. Congenital mitral valve disease almost always accompanies endocardial cushion defect and is of hemodynamic consequence in 75 per cent of the cases.[18] Rheumatic involvement in endocardial cushion defect must be extremely rare and would be very difficult to recognize. Rheumatic mitral valve disease commonly takes the form of stenosis; incompetence is less frequent. The clinical diagnosis in the most severe cases is difficult. The left atrium is decompressed by the free communication between the left and right atria, thus minimizing the signs dependent upon a large diastolic gradient across the mitral valve, namely, a loud first sound, opening snap and long diastolic murmur with presystolic accentuation. None of our patients had the classic signs of mitral stenosis. Moreover, obstruction to flow through the mitral valve had the effect of increasing the left to right shunt so that the signs of the atrial septal defect dominated the clinical picture. It is probable that the signs of mitral stenosis become conspicuous only when the atrial septal defect is small, thereby permitting a rise in left atrial pressure and a mitral valve gradient. Recognition of mitral stenosis at catheterization may also be difficult because left and right atrial pressure equalize. If the left ventricle can be entered, the gradient across the mitral valve can be determined on a withdrawal tracing.

The presence of a high right atrial pressure and of atrial fibrillation should always alert one to the possibility of associated mitral stenosis. We have found radiologic evidence of left atrial enlargement only in patients with Lutembacher's syndrome and regard this as an important sign. The electrocardiogram has been of no help.

Mitral incompetence is recognized by the presence of a loud pansystolic murmur

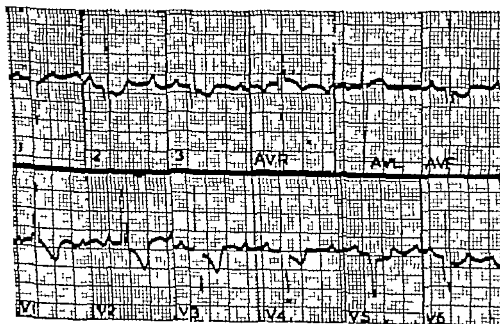


Fig. 6. Electrocardiogram from a patient with Lutembacher's syndrome associated with a large atrial septal defect at catheterization. Right axis deviation and severe right ventricular hypertrophy are present. The presence of large Q waves in the left ventricular leads indicated an additional ventricular septal defect which was confirmed at a second catheterization.

at the apex which is completely different from the pulmonary ejection murmur. It may be accompanied by a diastolic rumble. In the case of endocardial cushion defect the murmur tends to radiate more medially than it does in the case of rheumatic mitral incompetence. However, the two conditions will usually be differentiated by the electrocardiogram. Other congenital malformations of the mitral valve are occasionally encountered, particularly in the case of endocardial cushion defects. These includes conditions such as double or even triple mitral orifices.[1, 4, 47]

5. *Partial and total anomalous pulmonary venous drainage; single atrium.* These three conditions can present a clinical picture identical to that of atrial septal defect. Partial anomalous pulmonary venous drainage is usually associated with an atrial septal defect and is recognized at catheterization[44] (*vide supra*). It is fairly constantly present in a sinus venosus defect. Single or multiple veins may drain anomalously, with the right lung usually being involved. In the rare cases of partial anomalous pulmonary venous drainage with an intact atrial septum, splitting of the second sound has been reported to behave normally during respiration,[44] but this has not been a constant experience in our patients. If in addition to the signs of an atrial septal defect a continuous murmur is heard under the clavicle, usually the right one, and the patient is cyanotic, total anomalous pulmonary venous drainage can be diagnosed at the bedside. Occasionally, clinical cyanosis is absent and reliance can be placed on the radiologic findings (the "figure of eight" appearance of anomalous drainage into the superior vena cava[44] and the "scimitar" sign of drainage into the inferior vena cava[52]). Single atrium is often but not constantly associated with left axis deviation in the ECG and also cannot be distinguished except by special catheterization and angiocardiographic techniques. We have encountered cor triatriatum with an atrial septal defect at operation in a patient in whom the preoperative diagnosis was that of secundum septal defect.

6. *Atrial septal defect plus ventricular septal defects.* A secundum defect may be associated with the usual type of ventricular septal defect.[4] Clinically, the ventricular septal defect dominates the findings, whereas the atrial septal defect is recognized at cardiac catheterization. Tricuspid incompetence must be excluded. The electrocardiogram usually helps to differentiate this condition from an endocardial cushion defect. When the ventricular septal defect is large, severe pulmonary hypertension and reduced distensibility of the right ventricle are present. The atrial shunt therefore becomes right to left at a time when the ventricular shunt is still left to right. This leads to the paradox of central cyanosis associated with the persistence of a short murmur of ventricular septal defect and pulmonary plethora.[44] In the presence of a high peripheral arterial resistance (Eisenmenger's syndrome) the murmurs disappear and both the atrial and the ventricular septal defects may be completely missed unless sought for at catheterization. Persistent large Q waves in the left lateral precordial leads in cases of Eisenmenger atrial septal defect suggests this diagnosis (Fig. 6).

7. *Atrial septal defects in infancy.* Atrial septal defects of the secundum type are generally asymptomatic in infancy. When disability is present, an endocardial cushion defect is usually present. However, heart failure in infants with apparently uncomplicated secundum defects is well documented,[53] and unless one is aware of this, a potentially curable condition may be missed.

8. *Small atrial septal defects.* Most atrial septal defects are large; in fact, at operation the defect is seen generally to have a diameter of at least 2 cm. When an uncomplicated atrial septal defect is recognized at the bedside, the shunt is usually over 50 per cent and the defect large. Radiologically, shunts between 40 and 50 per cent can sometimes be detected,[18] but in the case of smaller defects the x-ray picture is normal. Small atrial septal defects, however, are uncommon.[44] Actually, this may not be so since small defects may be missed clinically and at necropsy. Generally, we have found small defects in association with mild pulmonary stenosis; the clinical presentation is that of mild pulmonary stenosis. Wide splitting of the second sound with a normal to loud pulmonary second sound and no

change in intensity of the pulmonary systolic murmur when amyl nitrite is inhaled may suggest this combination at the bedside.[38] Small atrial septal defects may also occur in cases of endocardial cushion defects with the clinical picture being that of severe mitral incompetence.[4] The defect may be completely missed unless careful catheterization is performed.

9. Bacterial endocarditis. Bacterial endocarditis complicating atrial septal defect usually indicates an endocardial cushion defect and is uncommon.[4] The abnormal valves or the ventricular septal defects are affected. Involvement of the atrial septal defect itself is extremely rare, with the secundum defect complicated by bacterial endocarditis being highly exceptional[39] (5 patients in all), and even in these cases the pulmonary or tricuspid valves have usually been affected. Paradoxical emboli and brain abscess are very rare hazards.

10. Rheumatic heart disease. Discussion of the subject would not be complete without making mention of acquired valvular disease. The physical signs produced by mitral, aortic, and tricuspid valve disease closely resemble those of endocardial cushion defect, and the condition of several of our patients in the medical outpatient department masqueraded for years as rheumatic heart disease. The major clues are the electrocardiogram and the radiologic evidence of pulmonary arterial plethora in contrast to pulmonary venous distention. A rare presentation is that of mitral incompetence with split mitral valves and a small atrial septal defect found at operation.[5] Secundum defects are most commonly confused with mitral stenosis because of the wide radiation of the tricuspid diastolic murmur to the apex and the signs of right ventricular overload. A particularly common mistake occurs during pregnancy when the circulatory changes are accentuated.

Surgery

In a condition which is generally known as uncomplicated ostium secundum defect a remarkably low mortality and morbidity is obligatory before operation can be recommended. This has been achieved in most good centers: the operative mortality has varied from 0 to 1 per cent depending on whether hypothermia or cardiopulmonary bypass was used. In our own Unit we have had no mortality in our first 97 patients. Generally speaking, operation is advised in patients with a left to right shunt of 50 per cent or more (this includes most patients whose condition is recognized clinically), and age is no barrier. When severe pulmonary hypertension is present the operative risks are greater, but provided that the dominant shunt is still left to right, operation is advisable.

When sinus venosus defects or anomalous pulmonary venous drainage is present, cardiac bypass is the method of choice, and profound hypothermia is often necessary with discontinuance of bypass while the defects are repaired. The mitral valve should always be felt, particularly when mitral stenosis is suspected, although this increases the risks of air embolism.

It must be appreciated that complete abolition of all left to right shunting cannot be guaranteed even with the most meticulous technique. A small insignificant shunt can be detected in at least 10 to 25 per cent of the patients if careful postoperative catheterization is performed.[33,34,37]

The only safe technique for surgical correction of endocardial cushion defect is whole body perfusion, with or without hypothermia. When a ventricular septal defect is absent, a mortality of 7 to 27 per cent[41] has been reported, which is acceptable when the severity of the condition and the poor life expectancy are considered. Particular care must be taken in correcting the mitral incompetence, in dividing abnormal chordal restraints and avoiding heart block, and a patch is always necessary. Some degree of mitral incompetence frequently persists after operation. In cases of endocardial cushion defects with ventricular septal defect the operative mortality is generally above 60 per cent and is dependent on the size of the defect and the pulmonary resistance. When the defect is large and the pulmonary resistance high the risks are prohibitive.

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

Diuretic therapy

Part III. Clinical use of mercurial diuretics

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All the mercurial diuretics available for parenteral use contain 39 mg. of mercury per cubic centimeter except mercaptomerin, which contains 30 mg. of mercury per cubic centimeter. The quantity of mercury in the compound appears to determine the effectiveness of the diuretic. Thus equal quantities of the various mercurial diuretics are comparable therapeutically. The maximal diuretic effect is achieved by 80 mg. of mercury, so that it is not necessary to give more than 2 c.c. of an organic mercurial at one time.

Increased diuresis is apparent within 1 to 2 hours after intramuscular injection, reaches a peak in 6 to 9 hours, and continues for 12 to 24 hours. Intravenous administration of the mercurial will accelerate the onset of diuresis, but mobilization of theophylline or mercaptan complexed mercurials from the intramuscular site is so rapid that the difference is slight. Only if the site of injection is edematous is absorption markedly delayed.

Mercaptomerin is the least irritating of the mercurials and can be given subcutaneously. Intravenous injection of all mercurials except mercaptomerin is hazardous and may cause sudden death from ventricular fibrillation due to direct action on the heart.

Inasmuch as most of the diuretic effect of a mercurial is completed in 12 hours, it would seem reasonable that administration every 12 hours would produce maximum continuing effect. However, such a schedule is both dangerous and unnecessary. Although 50 per cent of a mercurial is excreted in 3 hours and 75 to 95 per cent is usually excreted in 24 hours, measurable amounts can be found in the urine during the next 3 days. Thus administration of a mercurial every 12 hours will certainly produce accumulation and the danger of mercurialism, and its administration every 24 hours will *probably* do so even in the patient with reasonably normal renal function. In the presence of primary renal insufficiency or with severe congestive heart failure with diminished renal blood flow, the rate of excretion of a mercurial is much reduced and the hazard of mercurialism proportionately increased when the drug is given at frequent intervals. The failure of a patient to lose much weight with the first injection is suggestive of diminished renal blood flow and diminished glomerular filtration rate, hence involving a greater risk of mercurialism if further injections are given at short intervals.

Renal insufficiency is a relative contraindication to the use of mercurial diuretics

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They should not be used in patients with acute glomerulonephritis and acute renal shut down. With caution they can be used in cases of nephrotic syndrome and in congestive heart failure complicating the course of chronic renal insufficiency. In these situations transient renal effects produce no measurable lasting damage unless mercurialism is produced. There is however no simple clinical index of mercurial accumulation and impending mercurialism so that conservative infrequent use is the only protection.

Unresponsiveness to mercurial diuretics. The most important cause of unresponsiveness to mercurials is a diminished glomerular filtration rate. This is not always remediable but can be combated in two ways. (1) The first is by an attempt to increase the cardiac output, which results in greater renal blood flow, and also to use measures that further inhibit the tubular reabsorption of sodium. This can be accomplished to some extent by making certain that the patient is fully digitalized, in this way increasing cardiac output. Bed rest is important, especially for 8 hours after the injection of a mercurial, because the recumbent position regularly increases renal blood flow. The intravenous injection of 500 mg. of aminophylline 1 hour after the mercurial will increase cardiac output and renal blood flow and so increase the solute load to the tubules. (2) The second method is to add other diuretic drugs with different modes of action to further block tubular reabsorption. One of the thiazides can be used for this purpose. Spironolactones are also sometimes effective in this situation.

A dilutional hyponatremia and hypochloremia mediated by an antidiuretic hormone (ADH) may be the cause of unresponsiveness in patients with a reduced cardiac output and a low glomerular filtration rate. This should not be confused with the low salt syndrome induced acutely by excessive diuresis or with electrolyte depletion due to mercurials themselves. Hypochloremic alkalosis produced by chronic mercurial therapy can be corrected by giving 8 to 12 Gm. of ammonium chloride a day or 30 Gm. of lysine monohydrochloride a day for several days prior to and on the day of the injection of the mercurial.

Unresponsiveness can also be due to the inadvertent simultaneous administration of drugs which block diuresis. Morphine and other narcotics and possibly large doses of barbiturates can inhibit or interrupt mercurial diuresis by stimulation of ADH. Therefore, it is generally undesirable to give a mercurial if morphine is being used to treat pulmonary edema. Occasionally, mercurial diuresis may be partially blocked by acetophenetidin, acetanilide, antipyrine and aminopyrine. Although the mechanism is unknown, the recently described nephrotoxicity of acetophenetidin may be a clue to a direct renal effect.

Because of the development of potent oral diuretics in recent years, the importance of mercurial diuretics has diminished. Nevertheless, there are a number of situations in which they remain extremely valuable. (1) The profound and prompt diuresis produced by mercurials gives a clear-cut end point in situations in which the response to a diuretic is used as an index of expanded extracellular space, as in the differentiation between cardiac and pulmonary asthma. (2) This same acute response makes mercurials very effective in quickly relieving very edematous and seriously ill patients. (3) They are certainly valuable when used in conjunction with the thiazides in the relatively unresponsive chronically ill cardiac patient. Because of the need for parenteral injection and because of the unevenness of such intermittent therapy, continuing therapy in the moderately ill cardiac patient is usually more conveniently accomplished by thiazides. (4) When the patient is unreliable or when the patient either cannot tolerate oral potassium supplements or has had hypokalemic complications despite potassium supplementation, it may be wise to use mercurials by injection intermittently. (5) When a patient develops clinical gout or when diabetes is aggravated by thiazides, the physician may choose to switch to intermittent mercurial diuretic therapy rather than counteract these complications with other drugs.

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Acute interstitial nephritis

Acute interstitial nephritis is rarely diagnosed today but was apparently a well recognized and common complication of scarlet fever and diphtheria at the end of the last century. Councilman defines the condition as an acute inflammation of the kidney characterized by cellular and fluid exudation in the *interstitial tissue* accompanied by but not dependent on degeneration of the tubular epithelium; the exudation is not purulent in character and the lesions may be both diffuse and focal. It seems likely that this condition was *one of the causes of* anuria which occurred in the early days of sulfonamide therapy although no comment was made on the similarity between the lesion produced by sulfonamides and that complicating infectious fevers. It seems fairly certain from the descriptions in the literature that acute tubular necrosis and acute interstitial nephritis were considered to be different degrees of severity of the same lesion. This is perhaps not surprising when the similarities of presentation of the two conditions are considered and it is remembered that the final diagnosis had to be made on postmortem material. There is evidence that acute interstitial nephritis is part of a generalized sensitivity reaction whether associated with bacterial infections or drug reactions.

It is of considerable interest therefore in view of the confusion which still exists that a case of acute interstitial nephritis attributable to drug sensitivity has been followed by means of renal function tests and biopsies to eventual recovery. This case helps to establish the two conditions as completely separate entities. It concerns a man treated with phenindione for typical angina pectoris who developed skin rash and hematuria after 17 days. He later became jaundiced and anuric with a blood urea level that rose to 375 mg./100 ml. Hemodialysis was required on two occasions. Diuresis commenced after 8 days of anuria and his condition gradually improved although renal function did not return to normal for 9 weeks.

During this recovery phase the most heart urinary finding was the inability to produce dilute urine even after water loading. During this period the urine osmolality rose as high as 600 mOsm per kilogram and was persistently higher than the serum osmolality. This finding is the converse of that in acute tubular necrosis wherein there is an inability to concentrate the urine and the urine osmolality follows closely that of the plasma.

The histologic changes on renal biopsy in this case are similar to the previous descriptions. The characteristic feature is the very intense widespread inflammatory cell infiltration of the kidney consisting mainly of lymphocytes, plasma cells and eosinophils. Necrosis of renal tubular epithelium with early regeneration can be found but it is not a dominant feature. In sections stained for basement membranes there appears to be a patchy dissolution of the tubular membrane often associated with focal increase in the inflammatory cells. This picture is very different from the changes seen in acute tubular necrosis wherein renal biopsy shows relatively minor changes compared with the degree of functional disturbance.[2] The inflammatory cell infiltration in acute tubular necrosis seems to be related to the necrosis and is therefore focal and most marked in the subcortical *zone of the medulla. In interstitial nephritis it is far* more extensive than would be expected if it were purely secondary to the tubular necrosis. The glomeruli in both conditions are unaffected.

The second biopsy made during the *recovery* phase of the disease is interesting for although renal function indicated a return to normal there is obviously permanent scarring. The picture of fibrosis, focal lymphocytic infiltration and an endarteritis could easily have been passed as chronic pyelonephritis although at no time during the illness was positive urine culture obtained and the biopsy needles remained sterile. Could cases of chronic pyelonephritis with persistently negative urine culture have a similar etiology? This question can only be answered by prolonged follow up of cases of this type and it seems important that physicians should be more aware of the condition and its differentiation both from true infective chronic pyelonephritis and from acute tubular necrosis. It may well be found that minor degrees of acute interstitial nephritis are not so rare as they seem to be at the moment.

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Electrocardiographic studies in patients with an artificial pacemaker

Interest in the Adams Stokes syndrome has greatly increased since the development of effective treatment by artificial electrical stimulation of the heart and the appearance of methods for closed chest defibrillation A review of the published work and a report of our material has been published earlier A major achievement in the treatment of Adams Stokes syndrome has been the development of closed-chest cardiac massage We have employed this method in about 70 patients in a medical ward more than half of them survived and about 20 per cent have been discharged

The treatment of Adams Stokes syndrome by an artificial pacemaker with electrodes placed directly on the myocardium has become an accepted procedure

We have used in 8 patients a pacemaker described by Chardack and associates and in 2 patients the Elema type developed by Elmqvist Both of these pacemakers are transistorized and subcutaneously implantable

Chardack and associates favor a stimulus rate of 60 per minute I find a stimulus rate of about 75 per minute to be more satisfactory A still higher rate is preferable in certain cases in which a high idiocardiac rate is complicated by bouts of tachycardia

One argument against a low stimulus rate is that when the rate of the patient rhythm is higher than that of the pacemaker interference between the two rhythms will frequently appear and will be especially pronounced with exercise This interference might result in ventricular fibrillation if the artificial stimulus fall in the vulnerable period Dittmar and associates[4] stated that when the pacemaker stimulus appeared in the T wave multiple ventricular extrasystoles were sometimes seen these authors thought that the sudden death of one of their patients was caused by ventricular fibrillation due to the artificial pacemaker

During prolonged cardiographic recording (1½ hours in each patient) in 3 patients with an artificial pacemaker I determined the distribution of artificial stimuli in the idiocardiac ventricular complex The patients own idiocardiac ventricular complexes and the diastolic period afterward were divided into

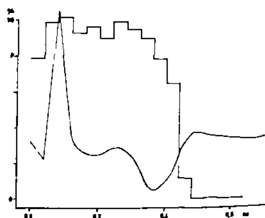


Fig 1 Percentage of artificial pacemaking stimuli (vertical axis) plotted against time intervals of the QRS-T complex of the spontaneous beats (horizontal axis) The stimuli from the artificial pacemaker appear mainly during the QRS complex and S-T segment of the spontaneous beats Each short horizontal line has a duration of 0 04 sec and shows what percentage of the total number of artificial stimuli fall during the various time intervals from the beginning of the idiocardiac QRS complex (based on 4 403 observations)

*The Chardack pacemaker ... Medtronic ... Minneapolis Minn ... and the Elema type by Elema Schonander Stockholm Solna Sweden

Table I Cardiac catheterization results at different ventricular rates

Parameter	Ventricular rate before operation (77 per minute)		Ventricular rate after operation (60 per minute)		
	Rest	*8 Minutes of exercise*	*Rest*	*8 Minutes of exercise*	*11 Minutes after exercise*
Cardiac output (L./min.)	5.3	6.4	4.7	9.5	4.0
Stroke volume (ml./min.)	230	370	78	158	67
Arteriovenous difference (vol. %)	4.5	7.2	5.1	6.2	5.8
Pulse pressure (mm. Hg)	143	160	3	90	71
Mean pressure (mm. Hg)	93	87	116	176	103
Oxygen consumption (ml./min.)	240	460	240	590	230

time intervals with a duration of 0.04 second from the beginning of the Q or R wave. The number of pacemaker stimuli falling in the different intervals was counted. The pacemaker stimuli were found to appear asynchronously, usually with a slight increase in frequency during the first two 0.04 sec. periods to a maximum 0.1 or 0.2 sec. after the beginning of the QRS complex. They then declined rapidly in frequency (Fig. 1). The most probable explanation for this phenomenon seems to be that the artificially induced beat depolarizes both the myocardial muscle and the conductive system. Then it would be necessary for the idioventricular pacemaker to begin a new repolarization cycle to continue gradually during diastole until a certain membrane potential is reached when depolarization occurs, initiating a myocardial contraction. This suggestion is supported by the fact that most of the spontaneous beats which occur after a pacemaker induced beat appear in late diastole. To avoid interference phenomena the rate of the artificial pacemaker should be high enough to suppress the idioventricular pacemaker.

When the artificial stimulus appeared in the beginning of the idioventricular ventricular complex, a fusion beat was seen, and when it appeared in the latter part of the T wave, an extrasystole was produced. In no case were there multiple extrasystoles or deformed ventricular complexes such as those described by Schwartz and associates. The present study indicates that direct stimulation of the myocardium with artificial pacemakers in the latter part of the ventricular complex does not result in lethal arrhythmias. Two of our patients who were operated upon died, but in both cases there were reasonable anatomic explanations for death. Both of these cases were included in the long term electrocardiographic studies described above. In no case did multiple extrasystoles appear when the pacemaker stimuli fell in the T wave.

Theoretically, the electrodes should be placed at the apex of the ventricle so as to let the contraction begin here and move toward the base, the aorta, and the pulmonary artery. If the electrodes are placed at the base, the contraction wave will move toward the apex and have an insufficient effect. This agrees with Corday's observation that the blood pressure was much lower if a ventricular tachycardia originated at the base than if it originated at the apex. But Van Tyn and MacLean found a significantly higher ventricular fibrillation threshold at the base than at the apex of the ventricle, and it was recently reported that in dogs there is no change in cardiac output whether the base or the apex is stimulated.

Through a needle in the brachial artery the blood pressure curve was simultaneously registered with the electrocardiogram in 6 of the patients. It was apparent that when a P wave closely preceded the ventricular complex, the pulse pressure and the systolic and diastolic pressures were higher than when the P wave fell in the ventricular complex, indicating that atrial contraction is of value in the diastolic filling of the ventricle. Two patients who developed atrial flutter after implantation of the artificial pacemaker did not show this phenomenon. The artificially produced pressure peaks at these beats reached the same level as peaks produced by single spontaneous beats, indicating that the artificial pacemaker is effective in spite of the aberrant conduction pathway.

It is essential for the discussion on the optimal stimulus rate to have hemodynamic data, such as stroke volume and cardiac output at rest and during exercise, at different stimulus rates. Such data from one of the patients is given in Table I. It is seen that the percentage increase in stroke volume was less at the lower rate, indicating that the patient used a great part of his reserve capacity even at rest, whereas the A-V difference was higher during exercise at the low heart rate. This observation indicates that it might be rewarding to study the metabolism of patients with a low heart rate and complete heart block. It is possible that these patients might develop new pathways for anaerobic metabolism. These hemodynamic and metabolic studies are in progress.

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Electrocardiographic evaluation of mitral valvotomy and restenosis

In mitral valve disease the electrocardiogram reveals left atrial enlargement resulting from left atrial hypertension and enlargement of one or both ventricles. Atrial fibrillation is seen in about 40 per cent of the patients. Pure or dominant mitral stenosis if severe is usually associated with some degree of right ventricular hypertrophy whereas dominant incompetence may produce signs of left ventricular hypertrophy.

The principal factor which governs the ventricular balance in mitral disease is the pulmonary vascular resistance and when this is elevated right ventricular hypertrophy tends to be seen irrespective of the degree of stenosis or incompetence. Nevertheless appreciable right ventricular hypertrophy on the electrocardiogram is more often seen with dominant mitral obstruction than with incompetence and evidence of left ventricular hypertrophy usually suggests either mitral incompetence or some other cardiac lesion causing left ventricular enlargement.

Many patients with critical mitral stenosis have but a modest increase in pulmonary vascular resistance the very high levels seen in congenital heart disease are unusual. Thus the electrocardiogram commonly indicates light or moderate rather than severe right ventricular hypertrophy. The total pulmonary vascular resistance always rises passively as a result of the left atrial hypertension produced by the mitral valve disease but an increase in arteriolar resistance due to reactive vasoconstriction also occurs in many cases—a high left atrial mean pressure (which is more common in stenosis than in incompetence) is the important precipitating factor. Thus serial electrocardiograms are a guide to rising left atrial pressure and increasing pulmonary vascular disorder.

It is well known that successful mitral valvotomy results in a fall in left atrial pressure and consequently in pulmonary vascular resistance although the resting cardiac output has been reported to be lower than before operation.[1] The electrocardiogram has been used to assess progress after valvotomy and also to aid in the detection of restenosis.

McInnes showed that electrocardiographic signs of severe right ventricular hypertrophy regressed after valvotomy in only 13 of 41 patients whereas Rodriguez Torres and associates found that the electrocardiogram returned to normal after operation in 59 per cent and improved in an additional 12 per cent of such patients. In patients with moderate pulmonary vascular disease and right ventricular hypertrophy the results of valvotomy are often better than in those with extreme pulmonary vascular disease but since the electrocardiogram in the former group may show little ventricular imbalance before operation improvement after valvotomy may be difficult to detect.

Changes in the electrocardiogram after valvotomy may be influenced by the development of restenosis. Demerdash and Goodwin have used electrocardiographic criteria to study the evolution of restenosis in 25 patients. Seven of the patients underwent a second valvotomy and the presence of tight stenosis was thus verified.

The clinical diagnosis of restenosis was based on a decrease in effort tolerance that followed an initial improvement after valvotomy, auscultatory signs of critical mitral obstruction and the absence of evidence of significant mitral incompetence.

Thirteen of the 25 patients (52 per cent) had evidence of right ventricular hypertrophy before valvotomy and 20 (80 per cent) at the time of restenosis. Right ventricular hypertrophy disappeared in 10 of the 13 patients (77 per cent) after the first valvotomy and in 12 of 14 (86 per cent) after the second valvotomy. The electrical axis showed interesting changes. After the first valvotomy all patients showed a shift to the left from a mean of +90 degrees to a mean of +64 degrees, whereas at the time of restenosis a shift to the right occurred which approximated closely the degree found before the first valvotomy. After the second valvotomy all except 2 patients showed a shift back to the left to a mean of +45 degrees. T waves tended to regress toward normal after valvotomy.

Before the first valvotomy 32 per cent of the patients had atrial fibrillation. After valvotomy the incidence increased to 48 per cent and at the time of restenosis it was 90 per cent.

The sum of the voltage of R in Lead V_5 and S in Lead V_1 was studied on the assumption that this value reflected left ventricular activity. The patients were divided into three groups according to the presence or absence of an additional lesion which might influence left ventricular function. The first group consisted of 10 patients who had tight mitral stenosis with minimal incompetence before and after valvotomy. The second group comprised 5 patients who developed moderate or severe incompetence after the first valvotomy and the third group consisted of 4 patients who had severe mitral stenosis with mild aortic valve disease or systemic hypertension.

The patients in all groups showed an increase in voltage after the first valvotomy, a reduction at the time of restenosis, and an increase again after the second valvotomy, but the initial voltage before the first valvotomy in the third group was double that in the other groups. The voltage after the first valvotomy was approximately the same in all groups but was greater after the second valvotomy in the second and third groups than in the first group. The range of values was too wide and the number of patients too small for statistical analysis, but the finding suggested that possibly the activity of the left ventricle was greater before the first valvotomy and after the second valvotomy in the patients with additional aortic valve disease and systemic hypertension than in those without.

An increase in voltage in R_{V5} and S_{V1} after valvotomy was attributed to increased activity of the left ventricle after release of mitral obstruction and the reduction in voltage at the time of restenosis to restriction of left ventricular inflow once more. Two patients did not show an increase in voltage after the second valvotomy, possibly because of previous coronary emboli in one and persistently elevated pulmonary vascular resistance in the other.

Thus the electrocardiogram may be of considerable value in following the progress of a patient after mitral valvotomy. Disappearance of signs of right ventricular hypertrophy indicates a successful valvotomy with a fall in pulmonary vascular resistance, whereas limited reduction in signs of right ventricular hypertrophy suggests that the pulmonary vascular disease has not fully remitted either as a result of fixed abnormalities in the pulmonary vascular bed or of a limited valvotomy. In this series 3 of 13 patients who did not show complete disappearance of right ventricular hypertrophy after the first valvotomy had evidence of considerable pulmonary hypertension at the time of restenosis. The incidence of right ventricular hypertrophy was higher at the time of restenosis than before the first valvotomy, which suggests more severe pulmonary vascular disease at that time. The incidence of right ventricular hypertrophy was higher than that in the series of Mounsey and Rodriguez Torres and associates, possibly because of the increased diagnostic value provided by the use of Lead V_1.

The shift in electrical axis to the left after successful valvotomy and again to the right when restenosis is occurring appears to be a sensitive index of changes in right ventricular hypertrophy and emphasizes the value of serial electrocardiograms at regular intervals after valvotomy when considered in conjunction with the clinical picture and history. Thus a patient who obtains marked improvement symptomatically and objectively for some years after valvotomy and then begins to deteriorate with signs of mitral obstruction and a shift of axis toward the right is highly likely to have developed restenosis. By contrast, a patient who obtains little improvement from valvotomy and deteriorates after a short interval without any change in axis or reduction in right ventricular hypertrophy may well have significant mitral insufficiency. It must be realized, however, that a single electrocardiogram would not be of great value in diagnosing restenosis or mitral incompetence, since a shift of the axis to the left after operation might indicate either a successful valvotomy or mitral incompetence. But subsequent serial electrocardiograms which showed a shift of the axis to the right would suggest restenosis unless a high pulmonary vascular resistance with marked right ventricular hypertrophy had developed in response to severe mitral incompetence rather than to severe stenosis. This emphasizes the fact that the electrocardiographic changes in mitral stenosis are dependent upon the pulmonary vascular resistance rather than upon the state of the mitral valve. Thus it is all the more important to consider the electrocardiogram not in isolation but in the light of all the clinical and hemodynamic data available.

Reduction in the P wave abnormalities after valvotomy may be regarded as useful signs of reduction in left and often in right atrial pressures resulting from relief of mitral obstruction. But the much higher incidence of atrial fibrillation at the time of restenosis largely invalidates a study of the P wave as a guide to restenosis. The higher incidence of atrial fibrillation with restenosis may reflect increased damage to the atrial wall because the patient's life span has been prolonged by the valvotomy and also the progressive nature of the rheumatic disorder.

It might be suggested that restenosis is improbable in the presence of sinus rhythm, which indicates that some other cause for recurrence of symptoms should be sought. It would be unwise to dogma

ruling was through the wrist because if it were through the hands there would not be adequate support by the tissues to prevent tearing by the weight of the body i frequently mentioned and does indeed suggest that there was considerable tension exerted on the arms However some ancient authors do report that the hands were the part transfixed [8] and thi would make much weight bearing unlikely The role of the crotch piece (edu lum) even less clear In the first place it ppears that thi device is mentioned only by Chri tian authors —an inexplicable fact If however it wa commonly used and it did partially upport the weight of the body as usually a umed then it would somewhat relieve traction and stretching of the arm Whether or not the crotch piece en couraged the victim to slump more than would be the case without it is problematical

4 Terminal events After a period of time on the cross and if the ictim were still alive he was often dispatched with a sword (Psalm XXII 20) or spear thru t One need not debate the cause of death in those cases The uncertain ritual of break ing the legs (crurifragium or skelokopia) has been p oposed as hastening death by suffocation because after the legs were broken the ictim could no longer lift himself up for relief and an intermitt ng stretch ing of the muscles of respiration would follow Breaking the leg as a form of pun hment is fre quently mentioned but it is doubtful whether this was a fixed part of the crucifixion ritual Pilate s ordering of the breaking of the legs of the criminal may well have merely been a supererogatory punish ment [4] and in other cases the legs were broken after the victim was taken down from the cross This ex traordinary act was p obably to prevent any victim with hared of l fe still in him from crawling away Cleaning up was frequently accomplished by roam ing packs of wild dogs and the choice of a site of crucifixion outside the wall of a city wa tactically contrived to take ad antage of this sanitary con venience Sometimes the subject was eaten while alive and still on the cross by wild beasts

5 T me the cross nd opinion of ancients on cause of death Death usually occurred after a few day on the cross not after 3 to 4 hours The death of Jesus after ju t 6 hours provoked surpri e and Pilate marvelled if He were already dead nd calling unto h m the centurion he asked him whether He had been any while dead (Ma k XV 44) Al th ugh survival for 2 to 3 day as not uncommon Lipsius cites two unu ual cases in which the victims lived 9 days on the cros Pain xhaustion and starv ti wc stated to be the cau e of death by cruci xion if the end had not been hastened by some other means

The facts all appear to be consistent with the traditional interpretation of the mechanism of death Scourging produced physical exhau tion and shock carrying the cro further weakened the victim and then hanging on the cross led to hypoten ion circulatory collapse and death The extent of scourging may well have determined how long the period of agony on the cro would last Pain thirst and starvation all contributed and frequently the subject wa d patched by a thru t from a legionnaire The challenging hypothe that d ath came to the crucified ictim through suffocation is not supported but neither t ex cluded by the fact of any historical account However the new hypothesis does leave unmen t ned one aspect of the mechanism of normal ventilation Wouldn t diaphragmatic contraction suffice even w th paralysis of the chest wall So says the ingenious and learned Dr Thomas Browne (Misc Writings) Concerning the motion (of the d ph agm) hereof I am layne to make this distich for my memorie

Contrahit exque cano rectum est dum
spiritu intra t
Lax t ex Pectoque c num est dum
spiritus exit

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Letter to the Editor

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To the Editor

I was very much interested to read the annotation entitled The Cervical Venous Hum in the *American Heart Journal* January 1964 by Noble O Fowler and Richard Gause

Here we have had the opportunity of studying a large number of cases of cervical venous hum occurring in the course of iron-deficiency anemia secondary to ancylostomiatic infection The venous hum is loudest when the hemoglobin level is lowest and vice versa As a matter of fact the venous hum disappears when the hemoglobin level reaches 9 to 10 Gm per cent This continuous murmur becomes more prominent after exercise After the inhalation of amyl nitrite the hum becomes less obvious

P K Krishnankutty MD (Madras) MRCP
MRCP (Edin) MRCP (Glas)

Book reviews

SEARCH THE SCRIPTURES By Robert B Greenblatt MD Medical College of Georgia Augusta Ga Philadelphia 1963 J B Lippincott Company 127 pages Price $4

This small book concerned with medical practices and concepts which originated from the Bible is interesting and entertaining Among the many interesting things discussed are the origin and reasons for such practices as circumcision fasting use of sugar in therapy society's attitude toward the aged why women's garments should differ from those of men as well as others This is a nice book written for the layman as well as the physician

ANESTHESIA FOR SURGERY OF THE HEART By Kenneth K Keown MD FACA Professor of Anesthesiology University of Missouri School of Medicine Columbia Mo Springfield Ill 1963 Charles C Thomas Publisher 205 pages Price $7 75

This book touches the high points of heart surgery as it is viewed by the anesthesiologist The data on cardiac catheterization are well presented and the chapter on cardiac irregularities covers the areas of most concern to the anesthesiologist Many aspects of heart disease are dealt with in rather cursory fashion for instance the chapter on radiologic contributions to the diagnosis of heart disease contains no illustrations The only discussion of the pump oxygenator and its use deals with the Mayo-Gibbon device which is probably the least commonly used of various pump oxygenators in this country

This book might be useful to anesthesiologists in training who want a concise review of the general field of cardiac surgery

WE MET AT BART'S By Geoffrey Bourne London 1963 Frederick Muller Ltd 288 pages

This is the autobiography of one of the prominent cardiologists of London It traces his experiences and impressions through his days as student house physician and specialist at one of the great and oldest hospitals of the world As indicated in the book some of the outstanding contributions to medicine were from Bart (St Bartholomew Hospital of London) Dr Bourne gives the reader a glimpse not only of the medical life at Bart's but of that at Harley Street as well His book provides insight into the problems of teaching practice and the care of patients at Bart's and as a matter of fact in all of London as well The book contains some interesting photographs of the prominent physicians at Bart's and also of the Hospital itself

This is a good book which should prove interesting to nonmedical as well as medical readers It is a summary of the experiences and impressions of Dr Bourne whose clinical observations are acute

CIRCULATORY ANALOG COMPUTERS Edited by A Noordergraaf G N Jager and N Westerhof Amsterdam 1964 North Holland Publishing Company 141 pages Price $4 75

This small monograph contains the Proceedings of a Symposium on the Development of Analog Computers in the Study of the Mammalian Circulatory System held April 19 and 20 1962 in Zeist Holland Altogether 9 papers were read dealing with pulsatile pressure-flow relationships regulatory mechanisms of the circulation wave propagation and elastic properties of arteries The selection consists of a fair repre

entation of present activities in this field. As in most conference Proceedings, the subject is not completely covered because of limitation in the number and interest of participants. Discussions are reproduced verbatim, which leads to a certain participation by the reader.

Analog computation ... based on circulatory model. Most participants of the symposium stressed the fact that much information on physical properties and parameters is still incomplete. The accuracy of mathematical models and the results of computation are limited by a lack of information on physical properties and dynamic behavior of the organ systems involved. The monograph can be recommended to the reader who already possesses familiarity with the subject. He will find the reading stimulating.

CLINICAL DISORDERS OF THE HEART BEAT. By Samuel Bellet, M.D., Professor of Clinical Cardiology, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pa. Ed. 2. Philadelphia, 1963, Lea & Febiger, 1105 pages. Price $28.

This monumental work is presented in seven sections. Section 1, the Introduction, deals with the anatomic, physiologic, and hemodynamic considerations in the arrhythmias. Section 2 offers a general discussion of the etiology, classification, clinical finding, and therapy of the rhythm disorders. Section 3 is a detailed discussion of the individual arrhythmias covering almost 500 pages of the text. Section 4 deals with general diagnostic procedures, including methodology in electrocardiographic diagnosis. In Section 5, the various arrhythmias peculiar to certain clinical states are presented in detail. These include such conditions as syncope, exercise, pregnancy, congenital heart disease, rheumatic fever, various metabolic abnormalities, and several others. Section 6 covers the drug therapy of arrhythmias. All important drugs are noted along with their pharmacologic actions, dosages, and toxic effects. Section 7 deals with means of therapy other than drugs, including carotid sinus pressure, artificial pacemakers, defibrillators, and cardioverters.

This book is one of the most complete works available on the subject of arrhythmias. It represents a great effort from a single author. The material is well presented, being only occasionally poorly organized in certain sections. Several errors, mostly of a minor nature, were noted. Paper, printing, and the reproduction of illustrations are excellent. Indexing is good. Complete references, including those of both current and historical interest, are included at the end of each chapter.

Since publication of this book, rapid advances have continued to be made in the field of the arrhythmias. The most notable of these has been the use of electrical means in the conversion of the rhythm disorders. Dr. Bellet's book includes a short chapter on these methods, but understandably the information provided is incomplete.

In general, this is an excellent book which covers the complex field of the arrhythmias in considerable detail. The reader is rewarded with both basic and practical information. This work can be highly recommended and should be available to all cardiologists.

CORONARY HEART DISEASE. A Personal Clinical Study. By Harold Feil, M.D., F.A.C.P., Clinical Professor Emeritus of Medicine, Western Reserve University, Cleveland, Ohio. Springfield, Ill., 1964, Charles C Thomas, Publisher, 148 pages. Price $6.50.

This book summarizes the personal experiences and ideas concerning coronary heart disease of an excellent cardiologist. Dr. Feil has devoted most of his life to cardiology and clinical research. He discusses the results of his studies of the case histories of 338 patients with angina pectoris and 1,516 patients with myocardial infarction as to incidence, survival, diagnosis, significant clinical features, and treatment.

This short, well-written book is recommended to medical students and clinicians who are interested in learning Dr. Feil's opinions and practices.

ÄTIOLOGIE UND KLINIK DER ARTERIELLEN UND VENÖSEN VERSCHLUSSKRANKHEITEN. (Verhandlungen der Deutschen Gesellschaft fur Kreislaufforschung, Bd. 29.) By Prof. Dr. Rudolf Thauer and Priv. Doz. Dr. Claus Albers. Darmstadt, 1963, Dr. Dietrich Steinkopff Verlag, 348 pages, 113 illustrations.

The main topic of this volume, representing the proceedings of the 29th Annual Meeting of the Deutsche Gesellschaft fur Kreislaufforschung (April 19-21, 1963), is arterial and venous occlusion (complete and incomplete). The thirty-four papers presented at that meeting and published with discussions give an excellent and up-to-date cross section of various occlusive vascular diseases in all important aspects: anatomic, pathologic, and biochemical bases, diagnosis, and therapy, along with extensive bibliographies. The topic "arterial and venous occlusion" includes a variety of vascular diseases and locations and, consequently, a variety of problems, methods, and clinical application.

A few arbitrarily selected highlights may be listed to convey a general idea of the content of the volume. The first article (J. Staubesand, pp. 1-16) discusses the anatomic structure of arteries as a basis for nutritional supply of the arterial wall. In larger arteries, the supply proceeds by diffusion through the intima and from the periphery through the vasa vasorum (which do not penetrate to the intima).

On the basis of electron microscopic studies, interruption in the fine structure of the cell membrane are discussed in relation to the molecular size of electrolytes and several organic substances (J. Staubesand, W. Rotter, p. 27).

Thrombus formation is discussed in several articles (A. Studer, p. 17; H. G. Lasch, p. 41;

J Zi ler p 67 St Wemler p 97 D Campa nacci et al p 148) with emphasis on its relation to atherosclero is

Of interest is I Lasat s finding (pp 52 58) that the muscles of the arterial wall can be de polarized without ontraction and that hista mine may produce a contraction of the depolar ized muscle

With regard to diagnostic method angiog raphy is discu sed by *H M Hame (p 106)* Of particular intere t is short paper by G Blumchen A Benmi ch and R J Bing (from Wayne State University Detroit Michigan p 161) on the use of rubidium for determina tion of the myocardial blood supply The method offers much promise for independent erification of ECG changes

The biochemical hanges which re ult from peripheral artery disease are discussed by K Hild (p 185) The lactate/pyruvat ratio in the femoral artery or ein was found to be a valu able index of peripheral hypoxia The ratio was lowest in 30 healthy persons and significantly higher in 90 patients with peripheral artery di ea e The differences were accentuated by work (pparently bicycle ergometer) L Con dorelli (p 197) found the ascular postural regulation impaired n patients with occlusive peripheral artery di ease In normal persons the peripheral blood flow not incre sed when the limb is rai ed by 30 to 45 degrees probably because of axon reflexes In 100 patients the postural regulation was partially or completely aboli hed

The plethysmographic recording of the bul bus orbital pul e (H Hager p 212) is an interest ing de elopment of ophthalmodynamography replacing the subjective ob ervation of the fundu by objective tracings In addition the method *makes determination of the pul* *e velocity* (carotid ophthalmic artery) po sible and thus widen the diagnostic application of the tech nique However i ual ophthalmodynamography satisfactory for empirical evaluation in most cases of carotid occlusion provided that it is done by a physician experienced in ophthalmos copy

The econd topic of thi volume is clinical cardiology The section consists of 15 highly diversified papers (pp 247 315) Of i terest i F Zaconto (Pari) experience with changes in peripheral circulation after conversion of ar rhythmias to sinus rhythm In most ca es there i an immediate and significant improvement independent of the etiology

In summary this olume contains much intere ting and aluable information It will be very useful for all physicians interested in the various aspects of cardiovascular disease and particularly peripheral vascular disea e

Announcements

Applied Office Psychiatry A graduate course in office psychiatry is being offered to physicians by the Institute of the Pennsylvania Ho pital 111 North 49th St Philadelphia 39 Pa

The course will consi t of twelve 4 hour weekly sessions beginning Oct 7 1964 At each es ion the student will observe through a one w y mirror patient being interviewed by an experienced p y chiatrist Patients will ha e problems commonly encountered in general medical practice

The faculty will include son e of the outstanding teachers of p ychiatry in the Philadelphia area

The topics to be covered in succe sive sessions are (1) Interview techniques (2) The anxious pa tient (3) The depressed *patient* (4) The m ltiple complainer (5) The impul ive patient (6) The accident prone patient (7) Frigidity impotence and other sexual di turbances (8) Overeating overdrinking and oversmoking (9) P ychosomatic aspect of gastrointe tinal di ease (10) Psychoso matic aspects of cardiovascular disease (11) Res piratory skin and mu culo skeletal p y ho phy i ological reactions (12) Psychiatric emergencies

A course in the Interpretation of Complex Arrhythmias will be giv n at Michael Reese Hos pital and Medical Center by Loui N Katz M D Richard Langendorf M D and Alfred Pick M D Th is an adv nced course intended only for ex perienced electrocardiographers The cla s will meet daily from 9 00 A M to 5 00 P M Nov 30 through Dec 5 1964 Regi tration limited to 30

Additional information and a copy of the lecture schedule may be obtained from M Bever*l y* Petzold Executive Secretary Cardiovascular In stitute Michael Reese Ho pital and Medical Center 29th St and Ellis Ave Chicago 16 *Ill*

American Heart Journal

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Editorial

Objective evaluation of therapy in transitory cerebral ischemia

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In any dynamic area of scientific endeavor it becomes necessary occasionally to assess critically the bases for current concepts. Such an attitude is particularly justifiable in regard to the present-day management of recurrent episodes of cerebral ischemia in patients with cerebral vascular disease, since there is so little universal agreement concerning the natural history of this disorder. Past experience indicates that untreated patients with transitory attacks of ischemia not infrequently may experience such episodes repeatedly over a prolonged interval without incurring demonstrable damage to cerebral tissue. Many such patients seem to recover completely ultimately, although even in these cases the long-term prognosis is unknown. In other patients minor neurological residua may eventually appear, and in still others frank and massive cerebral infarction may occur. A number of patients may exhibit inexorable diffuse cerebral deterioration, the progression of which appears to be independent of the frequency of the transitory episodes of ischemia.

In spite of the difficulties that a spontaneously variable course introduces in the evaluation of treatment of any disorder, in recent years several physiologically unrelated therapeutic modalities (anticoagulants, vasodilator agents, endarterectomy) have been advocated for the management of transitory episodes of cerebral ischemia. Examination of reported successes, however, reveals a peculiar statistical similarity which raises the suspicion that certain uncredited salutary factors may influence these results. Indeed, only three conclusions can be drawn from this phenomenon: (1) that any of the available therapeutic modalities, however different, may equally well arrest or compensate for or otherwise improve the course of the same disease; (2) that all active therapeutic efforts are completely ineffective and that reported clinical successes have been incidental and spontaneous; and (3) that each of the suggested methods of management owes its proportion of successes to the existence of certain patients particularly responsive to that modality. Although this last possibility

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carries with it the implication of an even distribution of responsive patients in spite of the need to assume this coincidence it would seem to provide the best hope of therapeutic selection of the specific modality best suited for the individual patient Such an approach however requires a standardized method of evaluation of the anatomic and physiologic abnormalities responsible for transitory attacks of cerebral ischemia At the present time in spite of the wide interest in the investigation and management of cerebral vascular disease there is surprisingly little uniformity in the assemblage of basic information so necessary for the interpretation of results Although various facets of cerebral circulatory dynamics are well within the reach of present investigative techniques it is disappointing that too often the latter are not employed

Although it is obvious that the surgical approach (endarterectomy) to the treatment of transitory attacks of cerebral ischemia requires angiographic study of the aortocranial vessels it is less widely appreciated that cerebral panangiography may be of value in the selection and evaluation of medical modalities It must be admitted that the shortcomings of radiographic studies of the cerebral vascular tree are manifold The physiologic significance of demonstrable lesions may be most difficult to assess since they may be *compensated by homeostatic mechanisms* to a degree not subject to estimation by x ray examination Moreover even an impressive stenotic or occlusive lesion of aortocranial vessels may be unrelated to the cerebral ischemic disorder which may actually depend upon the presence of an apparently minor or even undemonstrated intracranial vascular lesion In many cases angiography yields no reliable information in regard to the distribution of the intracranial blood flow nor does it provide quantitative data in regard to the hemodynamic effectiveness of the circle of Willis or whatever collateral sources of blood supply may or may not be demonstrated This and similar unresolved problems may eventually prove that the deficiencies of cerebral angiography particularly as applicable to evaluation of the medical management of cerebral vascular disease are due to inadequate correlation of radiographic findings with clinical observations and their resolution may well require more widespread use of the technique For example the inability to predict with satisfactory confidence the relative effectiveness of any medical therapeutic modality may be remedied in some degree by studies comparing the responses of patients who have multiple aortocranial lesions with those of patients who have single lesions and/or intracranial lesions Such vital information can be obtained only through panangiography Unfortunately none of the data so far submitted concerning the alleged efficacy of anticoagulants and vasodilator agents in cerebral vascular disease has been accompanied by sufficient panangiographic visualization to permit study of any possible relationship between type of vascular abnormality and therapeutic success or failure Furthermore there is virtually no information available in regard to angiographic follow up studies in such medically managed cases

Inasmuch as transitory episodes of cerebral ischemia are attributed to localized reduction of cerebral blood supply it should not be surprising that over all quantitative measurements commonly are found to show no significant reduction from normal values In fact it has been our observation that where such a reduction *is demonstrated diffuse cerebral* dysfunction is usually present and the transitory episodes of ischemia represent a complication rather than the major problem Moreover the value of estimation of total cerebral blood flow alone may further be called into question by the observation that cerebral blood flow can often be markedly reduced as by controlled hypotension in patients subject to transitory episodes of cerebral ischemia without provoking such attacks It is probable that in many of these instances compensation is accomplished *by vasodilatation* which occurs regionally or in collaterals which supply the marginally oxygenated area thereby protecting it from further ischemia in spite of the *relatively* brief experimental reduction in blood pressure It would appear therefore *that* information concerning the reactivity of

the cerebral vascular tree is often more pertinent in the evaluation of presently utilized therapeutic modalities than is quantitative estimation of total cerebral blood flow.

It has been observed that the cerebral vasodilator response to inhalation of 5 to 7 per cent carbon dioxide is not so predictably uniform in patients with cerebral vascular disease as it is in the normal population. Although some of the former patients show the same range of increase in cerebral blood flow as do normal subjects, others show a *less than normal response*, and in a significant number the inhalation of carbon dioxide is apparently without effect. Since even the latter patients demonstrate an increase in cerebral vascular resistance with hyperventilation, it may be concluded that the refractoriness to cerebral vasodilatation on inhalation of carbon dioxide is better attributable to pre-existing maximal dilatation of these vessels than to their pathologic rigidity. Carbon-dioxide challenge to the reactivity of the cerebral vessels is a relatively simple and safe procedure and may permit an important correlation between the responsiveness of these vessels and the results of any therapeutic approach, medical or surgical. For example, studies have indicated that patients with multiple degenerative lesions of the aortocranial vessels may nevertheless be capable of *significantly increasing cerebral oxygen delivery during the inhalation of carbon* dioxide, and one may question the need for or value of the surgical approach in these cases. Such doubts cannot be resolved, however, until the clinical results have been compared with those in similarly managed patients who appear to have exhausted the dilating capacity of their cerebral vessels.

Inasmuch as in our experience the *acute administration of* general vasodilators has been singularly ineffective in increasing cerebral blood flow (because of the concomitant reduction in blood pressure), it might be suggested that these agents may even be detrimental in patients whose cerebral vessels are already maximally dilated. Nevertheless, it would seem important to determine objectively whether there may be a difference in the clinical or quantitative effectiveness of general vasodilators between patients who do not respond to the inhalation of carbon dioxide and those whose cerebral vessels have retained significant reactivity.

It is not unreasonable to suppose that those patients who show no response to the inhalation of carbon dioxide may be more vulnerable than others to frequently repeated attacks of cerebral ischemia and even infarction (although this point, too, is worthy of investigation). If such is *indeed the case*, this propensity may facilitate more definitive evaluation than is presently available concerning the role of anticoagulants in the management of the disorder.

No doubt other modalities for collection of standardized data concerning the status of the cerebral circulation may be included in a format for evaluation of therapy in recurrent attacks of cerebral ischemia. One may mention ophthalmodynamometry, carotid compression tolerance, hypoxic, hypoglycemic, or hypotensive challenge of cerebral circulatory sufficiency, and techniques such as rheoencephalography, thermography, and isotope studies which may provide information concerning regional changes in cerebral blood flow. Unfortunately, these are not yet so well understood that interpretation of the results is likely to add materially to evaluation of treatment at the present time. Indeed, *the broad view of the problem of evaluation* of therapeutic modalities revolves upon uncertainty as to the value of investigative techniques in cerebral vascular insufficiency. Currently, we are faced with this impasse. There is reluctance to employ investigative techniques the results of which are of uncertain significance, and the significance of such results cannot be determined until the techniques are more widely used and until there is better correlation with anatomic, physiologic, and clinical observations. Obviously, the solution of this paradox lies in the continued undertaking of comprehensive studies rather than enthusiasm based upon narrow investigative approaches.

In summary, the similarity of successful results reported by advocates of unrelated therapeutic modalities in the management

of transitory episodes of cerebral ischemia warrants reservations in regard to these claims. There is a pressing need for a standardized method of evaluating the anatomic and physiologic abnormalities in cerebral vascular disease so that the results of treatment can be interpreted against the background of spontaneous variability and compared on a truly objective basis.

Cerebral panangiography, with all its shortcomings, is a necessary preliminary to assessment of the efficacy of agents advocated for medical management of cerebral vascular insufficiency, as well as of surgical treatment, and should be repeated for follow-up evaluation. Quantitative estimation of total cerebral blood flow yields results of dubious significance unless abnormally low. Knowledge of the reactivity of the cerebral vasculature is probably more important in the case of transitory episodes of cerebral ischemia. This can best be studied by measuring the response of the cerebral vascular resistance to the inhalation of 5 to 7 per cent carbon dioxide. At the present time, the most reasonable explanation for refractoriness to this agent is pre-existing maximal dilatation of the cerebral vessels. Patients whose cerebral hemodynamics are distinguished by this characteristic may well possess a peculiar vulnerability to frequent transitory episodes of ischemia or even cerebral infarction and may respond to a different degree or even in a different manner to therapeutic modalities than do patients who have a normal cerebral vascular reaction to carbon dioxide.

In the list of standardized data needed for evaluation of therapy of cerebral vascular insufficiency, there is room also for other types of challenge of cerebral hemodynamics and for methods of measuring regional cerebral blood flow. The relative importance of contribution of those investigative modalities now available remains to be determined, but must be determined for rational evaluation of management.

Clinical communications

Errors in voltage in multichannel ECG recordings using newer electrode materials

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With the recent installation of multichannel electrocardiograph recording in this department it was found that the measured voltages sometimes differed from those recorded from the same patient on a single channel machine. Furthermore, the disparity also varied with the choice of leads selected.

Investigation showed that the factor responsible for the apparent errors was the magnitude of skin contact resistance.

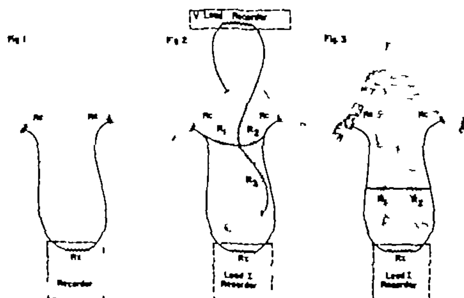
In order to evaluate this factor, measurements of skin contact resistance were made on 8 subjects with contact materials commonly used in this department, with the results shown in Table I. Three pairs of standard sized electrodes were applied on the forearms of each subject by a technician who used her usual techniques.

Since the resistance offered to an alternating current (AC) is of more importance in electrocardiography, impedances to AC currents at frequencies within the range present in the electrocardiogram were also measured. (Although in this annotation the more usual term *skin contact resistance* is used, this would be more correctly called *skin contact impedance*.)

The importance of low skin contact resistance can be understood from Fig. 1. The voltage appearing across R_1, the input resistance of the recorder, is reduced by the drop in voltage occurring across R, the contact resistance. In order that the true voltage be recorded, the skin contact resistance must be small compared with the input resistance of the recorder. When the string galvanometer, with its comparatively low input resistance, was in general use, low skin contact resistance was of vital importance but has become much less so with the use of vacuum tube recorders which have high input resistances. With the introduction of unipolar limb leads and leads derived from a central terminal, averaging resistors were inserted in the leads to minimize differences and changes in contact resistance to insure a consistent and stable reference point for the indifferent electrode. Most modern recorders use values of 5,000 ohms as the averaging resistor.

The disparity in voltages measured with a multichannel vacuum tube recorder with conventional input circuit design was found to be due to the low value of the averaging resistors when compared with the skin contact resistance. Fig. 2 shows the electrode connections for recording Lead I and a precordial V lead. This is redrawn in Fig. 3 to show the effective electrical circuit from which Lead I is derived. With the precordial lead in circuit the input resistance of the amplifier recording Lead I is effectively reduced by the shorting effect of R_1 and R. Since the

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Figs 1 3 See text

*Table I Resistance measurements (mean values and range for 8 subjects) between electrodes placed on the left and right arm using different electrode preparations**

		Abrasive saline jelly	Electrode cream	Alcohol sponge
DC re ta ce (kilohms)		4 4 (3 1—> 5 5)	113 (?? —> 400)	121 (30 —> 280)
AC impedan e (kilohms)	30 p s	3 ? (1 8—> 5 5)	14 8 (8 8—> ?40)	14 4 (9 6—> 18 8)
	at 60 c p	4 4 (3 2—> 6 6)	12 6 (8 ?—> 17 2)	14 3 (10 0—> 19 5)
	120 p s	3 1 (1 6—> 5 ?)	10 5 (8 1—> 14 2)	11 2 (6 5—> 15 4)

* ... ht ... pprecabl ... capaci ... ce th ... AC ... ECG ... measured

*Table II Voltages derived in Lead I (mV) in one subject with various lead selections using two electrode materials and different values of averaging resistor in the central terminal networks**

Avera n resistor	Lead I alone	Lead I with one V lead	Lead I with two V leads
		Abrasive saline jelly	
5k	1 14	0 65	0 44
50k	1 10	1 0	0 98
100k	1 12	1 14	1 0
		Electrode cream	
5k	1 05	0 24	0 12
0k	1 10	0 79	0 61
100k	1 05	1 00	0 79

*Al ... variance ... occurr ... ring the experim ... tal period ... electrode ... with the high-v ... eraging resistors.

value of R_1 plus R_2 was of similar magnitude to the contact resistance produced by a modern proprietary electrode cream the apparent voltage in Lead I was reduced. The errors were magnified by the addition of other leads involving averaging resistors (Table II).

We have eliminated these artefacts by reverting to the use of an abrasive saline jelly as a contact material and by increasing the value of each averaging resistor to 100 000 ohms.

The Frank vectorcardiographic lead system has shunt resistors of 330 000 ohms and 620 000 ohms across the outputs of the x and z axes, values high enough to prevent errors due to high electrode contact resistance.

Although little trouble is apparent in single channel recordings using the newer electrode creams, examination of our impedance measurements on one example of this type of preparation shows a range between subjects of greater magnitude than the value of averaging resistors commonly used in modern electrocardiographic recorders. This raises the question of the accuracy and consistency of the indifferent electrode when recording unipolar limb and chest leads. Since this work was completed it has been found that Schmitt, Okajima and Blaug[1] had similar findings and conclusions when they measured skin contact resistance using various contact preparations.

It would seem that the input circuit design of modern electrocardiographs should reflect the growing adoption of the newer electrode creams which, although offering some esthetic advantages, have less than ideal electrical properties.

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Cor triatriatum

Hemodynamic and angiocardiographic diagnosis

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In cor triatriatum an abnormal fibromuscular diaphragm divides the left atrium into a posterosuperior chamber which receives blood from the pulmonary veins and an anteroinferior chamber which communicates with the mitral valve and atrial appendage. This diaphragm contains one or occasionally several openings, the size of which determines the degree of obstruction to pulmonary venous return. The foramen ovale, which may be patent, may communicate with either the upper or lower chamber.

We know of no reported case in which angiocardiography has demonstrated the anatomic malformation of cor triatriatum. In view of this and the rarity of the condition, we report 3 cases. All 3 were studied by means of cardiac catheterization, and in 2 the angiocardiograms were diagnostic. Under direct vision all patients were operated on using total cardiopulmonary bypass.

Report of cases

Clinical, roentgenologic, and electrocardiographic findings are presented in Table I and hemodynamic findings in Table II. Plain roentgenograms are shown in Figs. 1 to 3. Brief notes pertinent to the individual cases follow.

Case 1. A diagnosis of cor triatriatum was considered prior to cardiac catheterization. After confirmation of the diagnosis, the patient was operated on by Dr. D. C. McGoon. The findings were those classically described for cor triatriatum. The single opening in the intra-atrial diaphragm measured 3 to 4 mm. in diameter and had thickened margins. The foramen ovale could not be identified. The mitral valve was normal.

The diaphragm was excised and the patient made an uneventful recovery.

Case 2. This patient, a youth of 19 years, was referred to the Mayo Clinic with a diagnosis of cor pulmonale on an asthmatic basis. In this case also the diagnosis of cor triatriatum was considered prior to cardiac catheterization. After confirmation of the diagnosis, the patient was operated on by Dr. J. W. Kirklin. The findings were those classically described for cor triatriatum. There were three small openings in the intra-atrial diaphragm, the margins of which were calcified. The foramen ovale was patent and was at the level of the intra-atrial septum.

The diaphragm was excised and the patient made an uneventful recovery.

Case 3. Angiocardiography was not performed during cardiac catheterization in this case because

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of the critical condition of the patient. A provisional diagnosis of congenital mitral stenosis was made; however, cor triatriatum was considered. She was operated on by Dr. D. C. McGoon and the findings were those classically described for cor triatriatum. The single hole in the intra-atrial diaphragm measured 6 to 7 mm. in diameter. The mitral valve was normal.

The diaphragm was excised, but the pulmonary arterial pressure did not fall. Initially, the patient did reasonably well, but he died suddenly on the first postoperative day. It was thought that residual pulmonary hypertension secondary to pulmonary vascular obstructive disease was the main factor contributing to death. Pulmonary vascular changes found at necropsy were graded 3 (on the basis of 1 to 6).

Results

All patients had increased pulmonary arterial and wedge pressures (Table II) indicating obstruction to pulmonary venous drainage. Left ventricular end diastolic pressures were normal. These findings indicated that the obstruction was at the level of the mitral valve, left atrium, or pulmonary veins, and for this reason

Table I. Summary of clinical, electrocardiographic and roentgenologic findings in 3 cases of cor triatriatum

	Case 1	Case 2	Case 3
Age	12½ mo	19½ y	3 y
Sex	Female	Male	Female
Height (inches)	24.5	64	36
(Percentile)	<3rd	—	5th
Weight (pounds)	14.7	98	25
(Percentile)	<3rd	—	3rd
History			
Duration of diminished exercise tolerance	12½ mo	13 y	3 mo
Duration of congestive heart failure	Few days	—	6 wk
Occurrence of pulmonary infections	Pneumonia twice; several upper respiratory tract infections	Pneumonia twice	Bronchopneumonia
Physical findings			
Murmurs (graded on basis of 1-6)	(1) Grade 2 systolic murmur lower L.S.B. (2) Grade 2 decrescendo early diastolic blow upper L.S.B.	(1) Grade 2 apical systolic murmur (2) Grade 2 decrescendo early diastolic blow upper L.S.B.	(1) Grade 2 systolic murmur lower L.S.B. and across to apex (2) Grade decrescendo early diastolic blow upper L.S.B. (3) Grade 2 apical mid diastolic murmur
Pulmonary valve closure	Accentuated 1+	Accentuated 2+	Accentuated 2+
Opening snap	Not present	Not present	Not present
Electrocardiographic findings			
Rhythm	Normal sinus	Atrial fibrillation	Normal sinus
Right ventricular hypertrophy	+	+	+
Atrial hypertrophy	+	−	+ (P mitrale)
Mean electrical axis of QRS complex	+ 130	+ 130	+ 130
Rotation of frontal plane loop	Clockwise	Clockwise	Clockwise
Roentgenographic findings			
Cardiothoracic ratio	57 per cent	53 per cent	60 per cent
Left atrial enlargement	+	+	+
Enlargement of main pulmonary artery	±	+	+
Pulmonary venous congestion	+	+	+

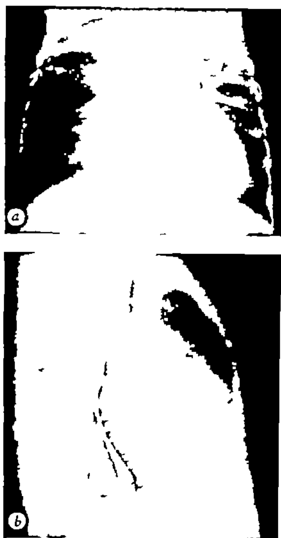


Fig 1 Case 1 Anteroposterior ( ) nd later 1 (b) roentgenogram of the chest h w pulm nary en ous engorgement and ardiac nd left trial en largement Also there enlargement of the main pulmonary artery Note the double contour at the right cardiac border due t left atrial enlargement

in 2 cases angiocardiography was per formed by injecting the contrast medium into the main pulmonary artery and pro gramming to outline the anatomy of the left heart Since angiocardiography per formed in this way is thought to carry a high ri k in the presence of severe pulmon ary vascular disease no angiocardiography was performed in Case 3 In Cases 1 and 2 angiocardiography was diagnostic in outlining the intra atrial diaphragm lying between the upper and lower left atrial chambers (Figs 4-6)

Case 2 was restudied by cardiac catheter ization 11 days postoperatively Consider able reduction in the pulmonary arterial and wedge pressures and in pulmonary



Fig 2 Case 2 Anteroposterior roentgenogram of the che t h w ardiac and left trial enlargement The pulmonary artery segment is prominent and there i pulmonary venous engorgement most marked i upper lobes Note the double contour at the right ardiac border



Fig 3 Case 3 Anteroposterior roentgenogram of the chest how con iderable cardiac enlar ement and changes due to pulmonary venous engorgement and edema

resistance had taken place but abnormal values indicated residual pulmonary vascular disease.

Comment

Cor triatriatum is a rare condition: 60 cases have been reported, in 5 of which the intra-atrial diaphragm involved the right atrium. The subject has been reviewed recently by Nrwavama.[3] In most cases the diagnosis has been made at necropsy. Failure to consider the diagnosis during life must be attributed to the rarity of the condition, since the clinical and hemodynamic picture is highly suggestive.

Hemodynamically, the condition mimics mitral stenosis and the clinical signs are therefore similar. Thus most patients who have been considered to be normal at birth have presented in the first or second year of life with a history of increasing breathlessness. They have signs of pulmonary hypertension with electrocardiographic evidence of right ventricular and possibly of left atrial hypertrophy. A mitral diastolic murmur, previously reported in only 3 cases,[3,4] was present in our Case 3. A systolic murmur maximal at the lower left sternal border, the usual finding, was present in our 3 cases. Moderate left atrial enlargement occurs[3,4] and was demonstrated roentgenographically in the 3 cases reported here. Left atrial enlargement was confirmed in Case 1 and Case 2 by measurement of the angiocardiograms according to the method of Arvidsson.[12] In Case 1, the volume of the left atrium (both chambers combined) measured 51 ml per square meter; in Case 2 it measured 89 ml per square meter (normal 24 ml per square meter ± 4.7).[12]

Table II. Hemodynamic data in 3 cases of cor triatriatum

	Case 1	*Case 2*		*Case 3*
Initial study				
Systemic index (L./min./M.²)	3.2	3.0		4.9
L.V. pressure (mm. Hg)	96/6–10	95/0–10		92/0
R.V. pressure (mm. Hg)	78/1–8	90/0–5		123/0–11
M.P.A. pressure (mm. Hg)	78/37	90/60		175/75
Wedge pressure (mm. Hg)	28/20	35/28		65/18
Pulmonary resistance (unit/M.²)				
Total	14.5	23		18.7
Arteriolar	7	13		9.5
At operation				
Before excision				
L.V. pressure (mm. Hg)	—	—		95/5 10
R.V. pressure (mm. Hg)	—	—		90/5 10
L.A.—upper chamber (mm. Hg)	40/15	—		47/27
After excision				
L.V. pressure (mm. Hg)	76/	—		88/8–15
R.V. pressure (mm. Hg)	55/			65/
L.A.—upper chamber (mm. Hg)	20/10			29/11
Final study				
Systemic index (L./min./M.²)		3.7	5.36	
L.V. pressure (mm. Hg)		—	—	
R.V. pressure (mm. Hg)		57/1–6	87/1 13	
M.P.A. pressure (mm. Hg)		53/24	87/44	
Wedge pressure (mm. Hg)		8/6	27/17	
Pulmonary resistance (unit/M.²)				
Total		10.5	10.8	
Arteriolar		8.9	8.6	

[illegible]
M.P.A. Main pulmonary artery.

pulmonary arteries were characterized by marked medial hypertrophy and intimal hyperplasia with an increase in subintimal fibrous tissue. No dilatation lesions were seen and the changes were therefore classified as Grade 3. The structure of the wall of the main pulmonary artery was of the fetal type which suggests that pulmonary hypertension had been present from birth.





Fig. 6. Case 3. Angiocardiograms before and after injection of contrast medium into the main pulmonary artery. a First film shows rapid reduction in calibre of the lower zone pulmonary arteries; these changes most marked on the right suggest pulmonary vascular disease and possible occlusion of the branches of the right lower lobe. b Late film shows left atrial enlargement and intra-atrial diaphragm as a linear filling defect (arrow).

Only 5 patients reported on have been studied postoperatively. In 4, pulmonary arterial and wedge pressures were normal at rest at 10, 6, 4[1] and 4 months postoperatively[4,7,8,9]. In one, a patient studied 2 years postoperatively and reported on by Redo and Goldberg,[9] pulmonary arterial and wedge pressures recorded during exercise were increased as was the pulmonary vascular resistance. Similar increases in pressure and in pulmonary vascular resistance during exercise were obtained in one of our patients (Case 2) when he was studied 11 days postoperatively. In Case 3 residual pulmonary vascular disease led to death on the first postoperative day. Clearly, therefore, pulmonary vascular disease can occur in this situation as a result of pulmonary venous obstruction and significant impedance to flow through the lung vessels and it can persist after complete removal of the obstructing diaphragm.

Summary

Three cases of cor triatriatum are reported. Each patient presented with breathlessness and had signs of pulmonary hypertension with electrocardiographic evidence of right ventricular overload.

Plain radiographs of the chest showed moderate left atrial enlargement and changes indicative of pulmonary venous engorgement. Left atrial enlargement was confirmed in 2 cases by angiocardiography and was quantitated by measurement of the left atrial volumes.

Hemodynamic studies revealed a considerable increase in the pulmonary arterial pressure (78 mm Hg systolic and 32 mm Hg diastolic to 125 mm Hg systolic and 75 mm Hg diastolic) and in the wedge pressure (28 mm Hg systolic and 20 mm Hg diastolic to 65 mm Hg systolic and 18 mm Hg diastolic) with normal left ventricular end diastolic pressures.

Angiocardiography was performed in 2 patients and in each the intra-atrial diaphragm was clearly demonstrated.

Removal of the left atrial diaphragm was successful in 2 patients. The third patient who had severe pulmonary vascular disease died on the first postoperative day.

Table III Hemodynamic data obtained 1 year (Case 1) and 9 months (Case 2) post operatively

	Case 1	Case 2	
		At rest	During exercise
Systemic index (L/min/M²)	4 4	3 9	6 8
M P A pressure (mm Hg)	48/21	41/13	63/27
Wedge pressure (mm Hg)	—	10/3	17/11
Pulmonary resistance (units/M²)			
Total	6 6	5 9	6 0
Arteriolar	—	2 3	3 9

M P A Main pulmonary artery

Addendum

Since preparation of this communication we have had the opportunity to restudy Cases 1 and 2 Case 1 was restudied 1 year after operation and Case 2 9 months after operation The data (Table III) demonstrated some residual pulmonary hypertension For Case 2 a further resolution of pulmonary vascular disease had occurred and values for pulmonary arteriolar resistance were now only minimally elevated

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The relation of the apical systolic murmur to mitral valve disease

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Systolic murmurs are frequently heard at the apex in mitral valve disease. Several causes have been recognized, the most common being mitral incompetence. Tricuspid systolic murmurs and aortic systolic murmurs often radiate to the apex and occasionally may be maximal at this site. When these three common causes are excluded, there remains the occasional apical systolic murmur regarded as *innocent* or *functional*, the cause of which is obscure.

When a systolic murmur cannot be detected at the apex, mitral incompetence can usually be excluded with confidence, since silent mitral incompetence is rare.[1] When a murmur is present, on the other hand, a fairly accurate clinical assessment can generally be made by paying attention to the intensity, duration, and radiation of the murmur. The influence of arrhythmias such as premature systoles or atrial fibrillation should also be noted. Simple maneuvers such as the effect of respiration, posture, exercise, and the Valsalva procedure on the intensity of the murmur may be of considerable help.[2,3] Lastly, the response of the murmur to vasoactive drugs may also be of value.[4]

It is the purpose of this paper to report on the findings in 450 patients subjected to operation, with particular reference to the presence or absence of an apical systolic murmur. The auscultatory findings during ventricular systole are particularly important, and if correctly assessed, the findings at operation can be predicted with a considerable degree of accuracy.

Material

The 450 patients in this study were consecutive patients seen and studied preoperatively by the author during an 11 year period in the Cardiac Clinic, Groote Schuur Hospital, Cape Town. All patients were fully examined, with special attention to the auscultatory findings. Electrocardiography and radiology (radioscopy or radiography, or both) were available in all patients. Cardiac catheterization was performed in approximately 10 per cent of the patients on whom closed mitral valvotomy was performed and in half the patients on whom bypass surgery was employed. The procedure was of value in assessing the severity of the hemodynamic abnormality, and the results were seldom in conflict with the anatomic diagnosis made on clinical grounds.

Routine phonocardiographic tracings were obtained on all patients by methods previously described.[5] A detailed analysis of the phonocardiographic findings with regard to the systolic murmur was not

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undertaken in view of the technical deficiency of the instruments used for recording purposes. Experience has shown that mitral systolic murmurs are often poorly recorded and difficult to separate from base-line artefacts and in any case are qualitative only.

The data therefore refer to clinical auscultatory observations only. All patients were examined repeatedly; the majority had been admitted to the medical wards for treatment prior to transfer for operation. In every case particular attention was paid to the duration of the systolic murmur when present, its intensity, radiation, and the response to respiration. Vasoactive drugs were seldom used. The intensity of the murmur was graded according to the method of Levine.

Operation was performed by 6 surgeons of the Cardio-Thoracic Unit. In every case the mitral valve was carefully palpated with particular reference to the size of the valve and the presence or absence of incompetence, and the findings were recorded during or immediately after operation. A rough attempt was made to quantitate the degree of incompetence; the amount of regurgitated blood was described as slight, moderate, or severe. The accuracy of these observations is therefore entirely dependent on the subjective sensations recorded by each particular surgeon at the time of operation. In 42 patients the valve was also carefully inspected while the heart was beating during cardiac bypass. Ten patients underwent both closed and bypass procedures performed in this institution.

Results

The results are shown in Table I. The hemodynamic disturbances were classified in four groups.

a. *Pure mitral stenosis* (356 patients) meant narrowing of the mitral valve without any palpable evidence of mitral incompetence. In 95 per cent of the patients the valve area measured less than 2 square centimeters.[8]

b. *Trivial mitral incompetence* (38 patients) indicated that a slight jet was felt during systole and was regarded by the surgeon to be of no hemodynamic consequence; it was often described as a "purr" rather than as a jet. In 72 per cent the valve area was less than 2 square centimeters.

c. *Mixed stenosis and incompetence* (34 patients) implied a significant degree of both stenosis and incompetence. Each

Table I. The relation of the apical systolic murmur to mitral valve disease

- 450 patients
  - No murmur 286
    - Pure MS — 280
    - Trivial silent MI — 5
    - Severe silent MI — 1
  - Apical murmur 164
    - Insignificant 50
      - Pure MS — 78
      - Trivial MI — 2
    - Tricuspid SM 37
      - Pure MS — 37
    - Mitral SM 97
      - Pure MS — 11
      - Trivial MI — 31
      - Significant MI — 33
      - Pure gross MI — 22

Pure MS = 356. Trivial MI = 38. MS and MI = 34. Pure MI = 22.

component varied considerably from case to case and no attempt was made to assess which was dominant. Attempts at quantitation was not possible at operation. Eighty nine per cent had valve areas between 1 and 3 square centimeter.

d. *Pure incompetence.* In 21 of the 22 patients the valves were inspected during bypass operation no stenosis being present.

1 Silent systole

In 286 patients who were subjected to mitral valvotomy no apical murmur was audible on repeated occasions. Pure mitral stenosis was found at operation in 280 of these. There were 5 patients in whom a slight but distinct incompetent jet was *reported by the surgeon prior to valvotomy.* In one incompetence was so severe that no attempt at valvotomy was made.

2 Apical systolic murmurs

There were 164 patients in whom apical systolic murmurs were heard. *In 30 the* murmur was Grade 1 2/6 in intensity, often short and regarded as insignificant or of aortic origin. *In 37 patients the systolic murmur at the apex was thought to* be tricuspid in origin and this was confirmed at operation pure mitral stenosis being present in every case.

A pansystolic murmur indicative of mitral incompetence was thought to be present in 97 patients.

In Fig. 1 the intensity of the *systolic murmur is plotted against the operative* findings. Nine patients had loud *mitral* systolic murmurs associated *with* loud tricuspid systolic murmurs which gave rise to confusion. In 4 the apical murmur was wrongly attributed to mitral *incompetence* and in 5 fusion of the *two murmurs* produced a loud murmur with little *mitral* incompetence. The loudest *murmurs* were associated with severe or significant mitral incompetence, soft murmurs generally indicated no or slight incompetence, a view long held by Levine.[7] A certain degree of overlap was inevitably encountered.

Discussion

On auscultation pure mitral stenosis was readily diagnosed by the presence of a loud first sound, opening snap and mid diastolic murmur with presystolic accentuation when the rhythm was sinus. Systole was silent. The diagnosis was made in 286 patients and confirmed in 280. In 5 trivial silent mitral incompetence was present and in only one was incompetence so severe that closed valvotomy was not even attempted. Thus silent mitral incompetence was rare. Logan and Turner[11] reported only one patient in 17. Harrison and Dexter[4] found 3 patients in a series of 52 subjects who had previously undergone mitral valvotomy.

Murmurs suggestive of tricuspid incompetence were present in 107 patients; characteristically there is a pansystolic murmur at the fourth left intercostal space and xiphisternal area. The intensity of the murmur varies considerably from case to case but characteristically becomes louder on inspiration. Sometimes it has a peculiar honking character.[10] With marked right ventricular dilatation the *murmur becomes widespread and is easily heard at the apex so that* it may be confused with mitral incompetence (37 of 76 patients). In one of our patients the murmur masqueraded as that of gross mitral incompetence for years before we appreciated *how widely* it could radiate and how loud it could be at the apex. The murmur *can be differentiated* by the fact that it is *louder at the* tricuspid area than at the mitral area and tails off rapidly as it reaches the axilla. In the axilla or posteriorly the sounds of pure mitral stenosis unassociated with a systolic murmur can be detected. Tricuspid murmurs generally appear in advanced heart disease in patients with marked cardiomegaly, pulmonary hypertension, atrial fibrillation and congestive cardiac failure. Repeated auscultation during energetic treatment for heart failure is most rewarding since in many cases the murmurs are functional and disappear with subsidence of heart *failure.* It is wise therefore never to diagnose mitral incompetence in cases *of this* kind but to treat and reassess the patient when the heart *failure has been* controlled. The diagnosis is really only difficult when mitral and tricuspid incompetence coexist. Pure mitral stenosis *was confirmed* at operation in 35 patients *in whom the* apical pansystolic *murmur* was attributed to tricuspid incompetence

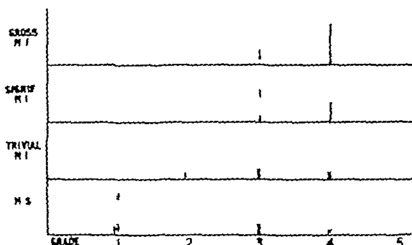


Fig. 1. The intensity of the systolic murmur has been plotted against the type of mitral valve lesion found at operation. In general, loud murmurs were associated with significant or gross incompetence, and soft murmurs with trivial or no incompetence. When tricuspid and mitral systolic murmurs were fused ( ) loud murmurs occurred with trivial or no incompetence found at operation.

A short apical systolic murmur, especially when soft, usually presents no difficulty. It can generally be attributed to an aortic systolic murmur conducted to the apex. Occasionally the murmur is long and the cause is obscure. In 30 patients with murmurs of this type, 28 were found to have pure mitral stenosis and 2 to have trivial mitral incompetence.

On auscultation, mitral incompetence was readily diagnosed by the almost invariable presence of a pansystolic regurgitant murmur, the intensity of which usually varied from Grade 2 to 4/6. The murmur commences with the first sound, which it may obscure, and runs right through systole to the aortic component of the second sound or even beyond it. It is maximal at the apex, high pitched, blowing in quality, and usually radiates to the axilla and posteriorly. Less commonly the jet is directed medially,[3] so that the murmur radiates up to the fourth left intercostal space and pulmonary area and less well posteriorly. It is not accentuated by inspiration and is markedly softened by amyl nitrite and intensified by vasopressor substances such as phenylephrine.

Generally, loud mitral systolic murmurs are associated with significant mitral regurgitation. In pure mitral incompetence there is usually no difficulty. Not only is the murmur characteristic and loud (Grade 4/6 or more) but there are all the associated signs of regurgitation, such as an enlarged hyperactive left ventricle, a loud third sound, and a short mid-diastolic murmur. Thus in 21 consecutive patients who underwent open heart operation, gross mitral incompetence was confirmed in all. Only one patient, early in the series, was thought to have mixed stenosis and incompetence, and at operation pure mitral incompetence was present.

When stenosis and incompetence are combined, however, there may be a wide spectrum, not only in the severity of the disease but also in the severity of each component. Here, too, a loud, widely radiating mitral systolic murmur generally betokens significant mitral incompetence, as was shown in 21 of 33 patients, the murmur being Grade 3/6 or more in intensity. A soft pansystolic murmur indicates slight or no mitral incompetence; the murmur was Grade 2 or less in 32 of 42 patients.

Unfortunately, the degree of mitral incompetence cannot always be assessed by the intensity of the systolic murmur. Loud murmurs may be found with little or no incompetence. Thus 10 patients who were thought to have trivial mitral incompetence were found to have pure mitral stenosis at operation. Either a slight degree of incompetence was missed by the

surgeon or there must be some other cause for the pansystolic murmur apart from mitral regurgitation. Significant mitral incompetence was diagnosed in 3 patients, in 2 of whom a trivial leak was found, and in one pure mitral stenosis during closed heart operation. This is almost certainly an underestimation of the frequency of this potential error since prior to the development of techniques of left heart catheterization and bypass surgery, selection for operation was very much more rigid, and patients who were thought to have significant mitral incompetence were generally not subjected to operation. With improvement in plastic procedures and valve replacement, virtually no patient is nowadays refused operation. It has become apparent that the degree of mitral incompetence can be grossly overassessed in a significant number of patients, especially in the presence of mixed mitral valve disease.

Conversely, severe incompetence may be present with little murmur. Underestimation of the degree of mitral incompetence, however, is less frequent. No patient who was considered to have trivial mitral incompetence was refused operation in this clinic. Only 2 of the 41 patients who were thought to have *trivial* mitral incompetence were found to have severe incompetence and were unsuitable for closed heart surgery.

It might be argued that there is too much overlap and that the clinical *assessment* of the degree of mitral incompetence is subject to such error that all patients with mitral systolic murmurs should be *investigated* by cardiac catheterization, dye dilution studies, and angiocardiography. This may well be desirable when adequate facilities and staff are available. Nevertheless it is as well to remember *that* even with these procedures the quantitative estimation of the degree of stenosis and incompetence is subject to error. Atrial pressure curves are notoriously unreliable. The injection of dye or radiopaque material into the left ventricle *must* take into account the effect of ectopics *of* correct placement of the catheter, and of uneven mixing.

It is our practice now to investigate all patients on whom open heart surgery is contemplated, and whenever there is any doubt as to the advisability of closed heart surgery. Whenever one valve is involved the clinical and catheter findings are seldom in conflict. In the presence of multiple valve disease, however, particularly aortic and mitral valve disease, the clinical assessment in our hands is still so unreliable that we regard investigation as obligatory.

In centers in which open heart surgery is practiced on all patients with mitral valve disease, a precise preoperative diagnosis may be academic. However, this is not practicable everywhere, particularly where pump facilities are limited and the operative material abundant, such as is the case in our Unit, nor is it necessarily desirable. This may mean that a certain number of patients, even after special investigation, will be found to have unsuitable valves or too much incompetence at closed heart operation. This may have to be accepted, provided that the percentage error is small. The importance of careful auscultation must not be underestimated. Despite occasional exceptions, the intensity of a pansystolic apical murmur is roughly related to the amount of backflow across the mitral valve. Pansystolic apical murmurs of unknown origin in the presence of pure mitral stenosis are uncommon, and silent mitral incompetence is distinctly rare.

Conclusions

1. Careful auscultation of systolic events at the apex is most rewarding, and the findings in 450 patients subjected to operation are presented. Accurate bedside diagnosis can be made in most patients without cardiac catheterization.

2. Systole was completely silent in 286 patients: 280 had pure mitral stenosis, 5 had trivial mitral incompetence, and one had severe mitral incompetence.

3. An insignificant or immaterial systolic murmur, often short, was heard in 30 patients: 28 of these had pure mitral stenosis and 2 had trivial mitral incompetence.

4. Tricuspid systolic murmurs heard at the apex can usually be readily differentiated from mitral incompetence and occurred in 10 per cent of the patients with pure mitral stenosis.

5. Severe mitral incompetence without

stenosis is readily recognized by the loud apical systolic murmur which radiates widely

6 When stenosis and incompetence are combined to make a diagnosis is difficult In general loud murmurs at the apex usually mean significant mitral incompetence and soft murmurs generally mean slight or trivial incompetence One is more likely to overestimate than underestimate the degree of incompetence from the intensity of the apical systolic murmur Investigation by cardiac catheterization and angiocardiography is particularly required in this group of patients and in general bypass surgery should be preferred to closed heart procedures

I wish to thank my colleagues in the Cardiac Clinic Dr W Beck Dr M Nellen Dr L Vogelpoel and Dr A Swanepoel for their help with the investigation of patients members of the staff of Groote Schuur Hospital for referring cases and the Superintendent Dr J G Burger for his permission to publish the finding I am particularly grateful to Dr Walter Phillips Profe or C N Barnard Dr K Hewitson Dr R Casserley Dr R Frater and D Muller Botha of the Department of Thoracic Surgery for performing most of the operations and recording their observations Thanks are due to the Council for Scientific and Industrial Research and the City Council of Cape Town for their financial support

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Correlation of the two-step exercise test (Master's test) and the hemodynamic findings in patients with mitral stenosis

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The two-step exercise test was introduced by Master and colleagues in 1929. Later electrocardiographic deviations from the normal after exercise were described in patients with coronary artery disease and various criteria were set to denote an abnormal test.[1]

In 1934 Karsner and Bayless reported that rheumatic fever may produce or hasten organic disease of the coronary arteries. However, there were reports to the contrary in the literature. In 1936 White[4] reported mitral stenosis in only 2 of 500 cases of angina pectoris. Similarly Hamilton and Thomson[5] and later Burgess and Ellis reported the low incidence of angina pectoris in patients with mitral stenosis.

The circulatory abnormalities that occur in patients with mitral stenosis and their effects on the over-all functional cardiac reserve have received comparatively little attention. In 1948 Hickam and Cargill[1] demonstrated the inability of the patient with mitral stenosis to increase cardiac output significantly with exercise. Later Master and associates inferred that coronary circulation may be impaired by stenosis of the mitral valve and that the two-step exercise test may be useful in determining the status of the coronary circulation in patients with rheumatic heart disease.

In 1959 Ramsey and Beeble[1] had 40 patients with mitral stenosis perform the two-step exercise test and found that 40 per cent of Class I, 76 per cent of Class II, and 100 per cent of Class III cardiac patients had a positive Master's test. They suggested that the electrocardiographic abnormalities which occur after exercise are due to myocardial ischemia.

This work was undertaken to find whether a correlation exists between the Master two-step exercise test and the various hemodynamic parameters obtained at catheterization of the right side of the heart in patients with mitral stenosis.

Materials and methods

Thirty-two patients with mitral stenosis were studied.

A complete history was obtained and physical examination performed on each patient by the same cardiologist. A twelve-lead electrocardiogram, cardiac fluoros-

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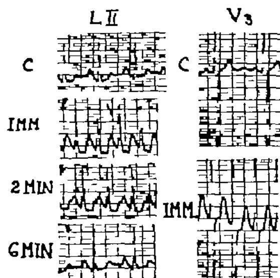


Fig 1 An example of the type and magnitude of S T depression in a patient considered to have a positive Master test *C* Control *IMM* Immediately after exercise

copy and films of the heart were subsequently obtained The patients were then classified according to the functional classification of the New York Heart Association [11]

Thirty one patients were in normal sinus rhythm and one patient had auricular fibrillation and was on maintenance dosage of digoxin

The ages of the patients ranged from 14 to 42 years Fifteen were males and seventeen were females

The Master two step exercise test was performed 3 hours after their last meal A base line electrocardiogram was taken prior to each test The number of steps climbed by each patient during a period of 90 seconds was determined from Master s tables Leads II V_3 V_4 and V were obtained immediately and at 2 4 and 6 minutes after exercise A test was considered to be positive when there was a depression of the RS T segment of more than 0 5 mm the depression being of the flat ischemic type[1] (Fig 1)

Catheterization of the right side of the heart was performed on all 32 patients by the usual technique A P23G B Statham strain gauge manometer and an Electronics for Medicine apparatus were used to measure and to record the pressure during catheterization of the right side of the heart Gas analysis and determination of the cardiac output and index were carried out in the usual way utilizing the Haldane Van Slyke [12] and Fick principle The patients were then exercised by straight leg raising Exercise was extended until the heart rates approximated those during the Master test The exercise varied from 1[1] to 2 minutes after which the pulmonary arterial pressure was immediately recorded

Mitral commissurotomy was performed on 29 of the 32 patients The mitral valve area was estimated by the surgeon s finger and the latter was measured against various sized holes with known surface areas

The following hemodynamic parameters obtained at catheterization of the right heart were tested against the results of the electrocardiographic exercise test (1) right ventricular diastolic pressure (2) pulmonary arterial pressure before and after exercise (3) mean pulmonary arterial pressure (4) wedge pressure (5) pulmonary vascular resistance (6) mitral valve area (as estimated at operation) (7) cardiac index

This study was analyzed statistically and the significance of the correlation was obtained utilizing the Student s *t* distribution tables for samples of less than 30 [14]

Results

Twenty one or 65 6 per cent of the 32 patients had a positive Master s test Their ages ranged between 14 and 42 years The mean age was 25 7 years Two of them had angina pectoris during exer

*Table I Classification of results of the Master test in 29 patients with mitral stenosis according to their functional cardiac classification**

Class	*Number of patients*	*Positive*	*Negative*	*Per cent positive*
II	5	2	3	40
III	24	16	8	66 7
Total	29	18	11	(? 1

Bec [illegible] few [illegible] number (3 pat [illegible]) Class IV [illegible] pat [illegible] ded

Table II Catheterization data and statistical analysis

Pressures (mm Hg)	Range		Mean		t	Degrees of freedom (N–2)	Probability	Critical value for 5 per cent level of confidence
	Positive Master's	Negative Master's	Positive Master's	Negative Master's				
Right ventricle Diastolic	0–8	0–8	4 6	4 5	0 170	30	0 9	t = 2 042
Wedge	15–35	15–33	27 2	24 45	1 175	27	0 25	t = 05
Pulmonary arterial mean prior to exercise	21–58	17–63	40 6	36 5	0 814	30	0 40	t = 2 042
Pulmonary arterial mean after exercise	27–87 5	25–73	51 4	45 7	0 588	16	0 56	t = 2 120
Magnitude of rise in mean pulmonary arterial pressure by exercise	1–37 5	4 40	14 1	17 43	0 540	16	0 59	t = 2 120

[illegible]

Table III Catheterization data and statistical analysis

	Range		Mean		t	Degrees of freedom (N 2)	Probability	Critical value for 5 per cent level of confidence
	Positive Master	Negative Master's	Positive Master's	Negative Master's				
Cardiac index (L /min /M)	1 7–4 1	2 3–3 6	3 15	2 86	1 370	30	0 20	t = 2 042
Mitral valve area (cm)	0 6–2 5	0 5 2 5	1 30	1 25	0 259	27	0 81	t 2 052
Pulmonary vascular resistance (dynes sec cm)	35 1 832	6 1 695	253 5	233	1 227	28	0 23	t 2 048

[illegible]

cise Eleven or 34 4 per cent of the patients had a negative Master's test Their ages ranged between 19 and 40 years The mean age was 27 8 years

Functionally these 32 patients were Class II Class IV cardiacs and the majority had dyspnea during exercise Five patients were Class cardiac patients and of these 2 or 40 per cent exhibited a positive Master's test Twenty four patients were Class III cardiacs and of these 14 or 66 7 per cent had a positive Master's test Finally 3 patients were Class IV cardiacs and all of them exhibited a positive Master's test These results are presented in Table I Because they were few in number the functional Class IV cardiac patients are excluded from presentation in Table I

Tables II and III show the results obtained at right heart catheterization for the group of patients with positive and negative Master tests Only the arithmetic mean and range for the various hemodynamic parameters are presented Heart rates obtained immediately after both types of exercise were comparable

The right hand side of the table shows the statistical analysis of the data obtained during right heart catheterization in both the group with negative and that with positive Master tests It is evident from Tables II and III that no significant difference exists between the means of various

hemodynamic findings obtained at right heart catheterization and positive or negative Master tests

Discussion

The mechanism of production of the RS T segment depression after exercise in some patients with mitral stenosis is not completely understood According to many authors this is thought to be based on relative or functional coronary insufficiency [10 11 17] Moreover these authors incriminate pulmonary hypertension as an important factor in the production of coronary insufficiency namely by increasing right ventricular work during exercise at a time when coronary perfusion is insufficient Our study did not show any correlation between the presence of coronary insufficiency and the elevation of pulmonary arterial pressure at rest and during exercise In a search for other factors that might interfere with the coronary circulation in these patients such as the area of the mitral valve left atrial pressure pulmonary vascular resistance and right ventricular diastolic pressure we found also no correlation between these and the results of the Master test Our work agrees with that of Ramsey and Beeble[10] concerning the increase in positivity of the Master test with the clinical deterioration in cardiac function as classified according to the functional classification of the New York Heart Association [11] However only 66 7 per cent of Class III patients had a positive test whereas Ramsey and Beeble found a positive test in 100 per cent of Class III cardiac patients

Coronary embolism was invoked as an important cause of angina pectoris in mitral stenosis Oakley and associates[17] documented 5 cases of coronary embolism in 42 patients with angina pectoris and mitral stenosis These authors also found no correlation between pulmonary vascular resistance cardiac index and angina pectoris

It is to be noted that about 81 7 per cent of patients with definite angina pectoris have a negative electrocardiographic exercise test [11] Therefore one might rightly assume that some of the group with the negative Master test may actually have coronary insufficiency this interferes with the final correlation of the different hemodynamic parameters and coronary flow

Summary

1 Thirty two patients with mitral stenosis subjected to catheterization of the right side of the heart and the two step exercise test were studied

2 There is an increasing chance that with deterioration of cardiac function the two step exercise test will be positive

3 No statistical correlation was found between the group of patients with a negative and that with a positive Master's test and the various hemodynamic parameters obtained at right heart catheterization

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Serum proteins in cyanotic and acyanotic congenital heart disease

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It was the purpose of this study to determine whether there is an abnormality of the serum protein electrophoretic pattern in patients with congenital heart disease, and whether sustained hypoxemia and diversion of the blood stream from the lungs, as a result of right to left shunts through congenital cardiac lesions, affects the formation and relative proportions of the serum protein fractions. To accomplish this, paper electrophoretic partition of the serum proteins has been performed in patients with cyanotic and acyanotic congenital heart disease and in control patients without heart disease who ranged in age from infancy to adolescence.

Patients and methods

Selection of patients. Twenty-two patients with cyanotic and 23 with acyanotic congenital heart disease observed in the course of a single year on the wards and in the clinics of the Cook County Childrens Hospital were studied. For comparison, 8 normal children who were less than 1 year of age and 20 patients with Down's syndrome (Mongolism) who were 2 to 16 years of age were studied simultaneously. The former were well babies in custodial care, and the latter were outpatients of the Levinson Clinic for Mentally Retarded Children of the Fantus Clinic of the Cook County Hospital. They represent nutritionally normal children in good health. Mongols with heart disease were excluded from study. The sex and race proportions were nearly alike in all groups. All were receiving a regular diet. None presented edema, congestive heart failure, proteinuria, hepatic disease, or other conditions that are known to affect the serum proteins. The classification of the patients with congenital heart disease who were studied is shown in Table I. The cyanotic patients all presented 3 to 4+ cyanosis, and arterial oxygen saturation, performed at the time of cardiac catheterization in 7 patients, ranged from 48 to 91 per cent.

Serum protein paper electrophoresis was performed according to the method of Block, Durrum, and Zweig.[1] For statistical analyses, since serum protein partition may change with age, the patients were divided into three groups: under 1 year of age, 2 to 6 years of age, and 7 to 16 years of age. The results were analyzed statistically by the "t" test for nonpaired samples.

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Results

Total proteins (*Table II*). A comparison of the concentration of total serum proteins in the patients with and without heart disease and in the cyanotic and acyanotic patients with congenital heart disease showed no significant statistical difference. The concentration of total proteins increased gradually with age but were within normal limits for each age group. Comparison of the different age groups showed no statistically significant difference.

Albumins. There was a statistically significant lesser concentration of serum albumins ($p < 0.01$) in the patients with heart disease than in the control subjects. There was no statistical difference between the cyanotic and acyanotic patients. There was also no significant statistical difference between the different age groups.

Alpha and beta globulins. The concentrations of both alpha 1 and beta globulins were significantly greater ($p < 0.05$) in the patients with congenital heart disease than in the control subjects. Furthermore the concentration of beta globulins in the patients with cyanosis was significantly larger ($p < 0.05$) than that in the acyanotic patients with congenital heart disease. There was no statistically significant differences between the alpha 2 globulin concentrations of the groups.

Gamma globulins. The concentration of gamma globulins was within normal limits for each age group studied. There were no significant differences between the cyanotic and acyanotic groups and between patients with and those without heart disease.

Table I. Classification of patients with congenital heart disease

Cyanotic	
Tetralogy of Fallot	8
Transposition of great vessels	5
A V communis	3
Taussig Bing anomaly	2
Tricuspid atresia	1
Levocardia	1
Anomalous pulmonary venous drainage	1
Truncus communis	1
	22
Acyanotic	
Ventricular septal defect	8
Patent ductus arteriosus	2
Ventricular septal defect and patent ductus arteriosus	1
Pulmonary stenosis	2
Atrial septal defect—ostium primum	2
Endocardial fibroelastosis	2
A V communis	2
Aortic stenosis	1
Coarctation of aorta	1
Congenital mitral regurgitation	1
Tetralogy of Fallot	1
	23

Table II. Electrophoretic partition of serum proteins in cyanotic and acyanotic congenital heart disease

Group	Age (yr)	Number of patients	Total proteins	Albumin	Alpha 1 globulin	Alpha 2 globulin	Beta globulin	Gamma globulin
			(Grams per 100 millilitres)					
Cyanotic congenital heart disease	<1	11	6.85±0.96	3.33±0.20	0.46±0.12	0.73±0.19	0.85±0.07	0.98±0.43
	2–6	4	7.10±0.57	3.67±0.72	0.43±0.06	0.65±0.16	1.3 ±0.51	1.03±0.28
	7–16	7	7.15±0.32	3.34±0.62	0.4 ±0.11	0.67±0.17	1.31±0.44	1.41±0.44
Acyanotic congenital heart disease	<1	7	5.93±1.05	3.19±0.47	0.48±0.12	0.65±0.15	0.[illegible]3±0.47	0.88±0.14
	2–6	9	6.51±0.83	3.55±0.35	0.46±0.11	0.7 ±0.18	0.[illegible]9±0.12	1.01±0.[illegible]9
	7–16	7	7.79±0.82	3.84±0.20	0.50±0.12	0.83+0.11	0.76±0.06	1.35±0.20
Control	<1	8	5.98±0.50	3.44±0.55	0.38±0.10	0.66±0.17	0.[illegible]0±0.17	0.80±0.21
	2–6	6	7.16±0.37	4.10±0.16	0.38±0.06	0.68±0.14	0.78±0.15	1.12±0.21
	7–16	14	7.34±0.50	4.16±0.47	0.35±0.09	0.63±0.10	0.78±0.14	1.13±0.30

Mean ± S.D.

Comments

Ueyama studied the serum protein electrophoretic pattern of 38 patients with congenital heart disease who were less than 15 years old. In 20 compensated patients the total protein concentration was normal or decreased, the albumins moderately decreased, the alpha globulins increased, and the beta and gamma globulins normal. In 18 decompensated patients there was an additional increase in the concentration of the gamma globulins. His findings in the compensated patients are confirmed by the present study, which in addition demonstrates an increase in the concentration of the beta globulins. Ueyama did not correlate the changes in the serum proteins with the absence or presence of cyanosis. Interestingly, Machetanz and Habeck[9] reported an increase in the concentration of the beta globulins in the cerebrospinal fluid proteins of cyanotic patients with congenital heart disease. They attributed this to an effect of chronic hypoxia on the tissue of the central nervous system. Since the spinal fluid proteins are largely derived from the blood proteins by filtration through the choroid plexus, it is also possible that the elevated beta globulins in the cerebrospinal fluid is a reflection of the serum protein composition in their patients. They did not, however, present data on the serum proteins.

The *mechanisms responsible for these* changes in the serum proteins is not clear. Hypoalbuminemia is observed often in decompensated heart disease regardless of etiology, and has been attributed to proteinuria, chronic passive congestion of the liver, cardiac cirrhosis, and malnutrition.[4-7] None of these factors are applicable to the patients of this study. Davidson and associates[3] have presented evidence that the severe hypoproteinemia observed in one patient with decompensated congenital heart disease and in 3 with pericarditis was due to a loss of albumin into the gastrointestinal tract. With recovery, however, the hypoalbuminemia was corrected. It is unlikely, therefore, that the same mechanism is operative in our patients. Hypoalbuminemia has also been reported in compensated cardiac inflammatory *conditions* such as endocarditis, myocarditis, and pericarditis,[7,8] but is generally absent in compensated hypertensive, arteriosclerotic, and valvular heart disease.[7]

The susceptibility to bacterial infection and the poor healing of wounds shown by the cyanotic patient with congenital heart disease suggested the possibility that an abnormality of the gamma globulins may be present. We were also curious to know whether hypoxemia had an effect on the well-known sequential changes in the formation of gamma globulins during infancy.[9,11] However, no abnormality of formation or electrophoretic pattern of the gamma globulins was observed. The sequential changes in the concentration of total proteins and other electrophoretic fractions were also unaltered.

There is a paucity of studies in the literature pertaining to the effect of chronic hypoxemia of any etiology, and of passage of the blood through the lung, on the electrophoretic characteristics of the serum proteins. Panno and Vitale[13] studied the blood proteins of rabbits subjected to decreasing degrees of barometric pressure. At a simulated altitude of 10,000 feet there was a decrease in the concentration of albumin and an increase in the concentrations of alpha 2 and beta globulin, whereas the other fractions were unchanged. Michel, Schulz, and Hartleb[14] reported that in the rabbit the concentrations *of alpha and beta globulin* decrease during passage through the lungs. Clearly, more such studies are needed to determine whether the changes in serum proteins in congenital heart disease, particularly in the cyanotic patient, are an adaptation to chronic hypoxemia or are due to the shunting lesion which allows blood to bypass the lung.

Summary

The serum proteins of patients with cyanotic and acyanotic congenital heart disease of different etiologies have been partitioned by paper electrophoresis and compared to those of nutritionally normal patients without heart disease. A lower concentration of the serum albumins and a greater concentration of the alpha 1 and beta globulins was found in the patients with congenital heart disease than in the control subjects. There was a further

statistically significant greater concentration of the beta globulins in the patients with cyanotic congenital heart disease than in those of the acyanotic group. The sequential changes with age of the concentrations of the total proteins and the electrophoretic fractions were not altered by the presence of chronic hypoxemia and right to left shunting of blood from the lung.

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Late peaking of the T wave as a digitalis effect

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During the past several years we have been impressed with the frequency of late spiking of the T wave in the electrocardiogram of patients receiving digitalis In other respects these T waves had the classic appearance associated with the effect of digitalis They showed a characteristic cupped depressed sagging or hammock shaped deformity of the RS T segment inversion of the T waves and shortening of the Q T interval The conjoint effect of these changes as illustrated in Leads V_3 V_4 V_5 and V_6 of the second strip (*1 20/58*) of Fig 1 is the subject of this communication The frequency of this composite change was studied in 100 consecutive electrocardiograms read during the year 1949 and in 100 consecutive tracings read in 1958 which were interpreted by the usual standards as showing a digitalis effect Twenty two of the 200 tracings showed this type of T wave 10 in 1949 and 12 in 1958 By contrast examination of 200 consecutive tracings recorded in patients who were not receiving and had not received digitalis during the previous month disclosed 3 with similar terminal peaking of the T waves and depression of the RS T segment One of these 3 patients had mild potassium intoxication the second had left bundle branch block and the third had angina pectoris and presumably subendocardial ischemia In nondigitalized individuals then this appearance was much less frequent and could be explained on other grounds Certainly such depression of the RS T segment and terminal peaking of the T wave is not characteristic of the electrocardiograms recorded in a population with normal hearts Nor is the RS T segment depression of potassium intoxication as such observed in the absence of some degree of intraventricular block In contrast to the change here described the peaking which characterizes uncomplicated potassium intoxication does not occur late in the T wave but is rather symmetrical or tent shaped

Our first inclination was to interpret this appearance as simply the combined effect

Table I Conditions associated with late spiking of T waves among 200 patients with digitalis effect in the electrocardiogram

Number of patients with late peaking of T (22)	21
Renal disease	9
Acidosis	2
K administration	3
Angina pectoris	1
None of these	9

*T[illegible] 1 [illegible] exceed 21 [illegible] some pat[ien]ts [we]re [associ]ated [with] more than one

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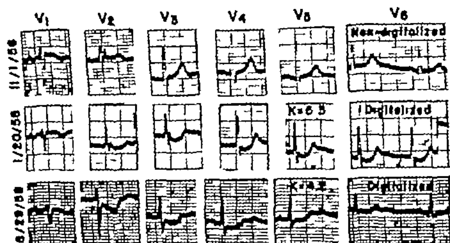


Fig. 1. Precordial leads with terminal peaking of T waves in patient with renal disease who was not receiving potassium. This change developed when K rose to 5.3 mEq./L. (1/20/58). The late peak disappeared when K fell to 4.7 (8/29/58).

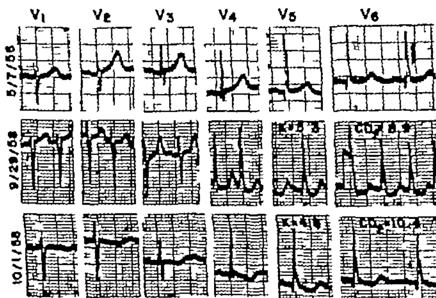


Fig. 2. Precordial leads showing transient peaking of T waves in patient with diabetic acidosis. Control tracing, recorded when patient was not receiving digitalis (5/ /56), within normal limits. Tracing recorded when patient had hyperkalemic acidosis and was receiving digitalis (9/29/58) shows sagging PS-T segment and late peaking of T waves. As K returned to within normal range the change disappeared although the patient was still acidotic and receiving digitalis (10/1/58).

of digitalis and electrolyte imbalance. Clinical and laboratory data were available for 21 of the 22 digitalized patients who showed this change (Table I). Of these, 9 had renal disease with slight to moderate uremia and elevation of the serum potassium concentration, 2 had acidosis (one renal, one diabetic), 3 were receiving maintenance potassium therapy, and 2 had angina pectoris.

Fig. 1 shows this change developing in a patient with renal impairment. He was not receiving potassium. His electrocardiogram was normal in November 1956. In January 1958, when he was digitalized, his serum

with uremia acidosis or hyperkalemia 3 were receiving potassium salts and 2 had angina pectoris Serial tracings indicated that peaking was generally transient and related to changing electrolyte balance occasionally persistent In 9 none of these factors was at play they had in common only the fact that they had heart disease and were receiving digitalis

Digitalis induces a loss of intracellular potassium This may have an effect upon the transmembrane potential similar to that caused by an increase in extracellular potassium The concomitance of intracellular decrease and extracellular increase in potassium concentration may explain these digitalis induced electrocardiographic changes

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The possible role of sex in digitalis tolerance

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Recent experimental work has shown differences in the tolerance of male and female animals to digitalis cardiotoxicity.[1]

The purpose of this study was to investigate a group of young adult patients with rheumatic heart disease in order to evaluate differences between the sexes in their reaction to cardiac glycosides.

Method and material

All clinical records of *patients aged 13 to 40 years* who were admitted to the Jackson Memorial Hospital, Miami, Florida, and the Veterans Administration Hospital, Coral Gables, Florida, between Jan. 1, 1958, and Dec. 31, 1961, with the diagnosis of rheumatic heart disease were reviewed. All electrocardiograms were reviewed and disturbances in rhythmicity recorded. Pertinent information was extracted from each clinical record and processed on Form 5081 IBM cards, tabulated and analyzed.

Results

I. Veterans Administration Hospital—Male patients

A. CLASSIFICATION OF PATIENTS AND CARDIAC RHYTHMS. A total of 31 male patients with 52 separate admissions fulfilled the criteria both of being under 40 years of age and of having a clinical diagnosis of rheumatic heart disease. This is an incidence of 1.7 admissions per patient during the 4 year period of study. Five patients (9 admissions) showed auricular flutter and/or fibrillation† consistently. Eight additional patients with 14 admissions were found to have other disorders of the heartbeat. In 4 of these 8 patients there were 9 admissions complicated by the development of arrhythmias attributed to digitalis cardiotoxicity. The other 4 patients with 5 admissions were observed to have an arrhythmia unrelated to the administration of digitalis. Table I outlines the clinical features of these patients with disorders of the heartbeat other than auricular fibrillation.

B. AGE. The average age of the patients was 35 years (range, 20 to 40 years). This did not differ materially between the patients with normal sinus rhythm (35.1 years), those with auricular fibrillation (35.3 years), and those with other arrhythmias (34.7 years). In the last group patients with digitalis-induced arrhythmias averaged 33.3 years.

C. DURATION OF DISEASE. The duration of rheumatic heart disease in the patients with normal sinus rhythm, auricular fibril-

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Table I Veterans Administration Hospital Clinical findings in male patients with rheumatic heart disease

Patient	Number of admissions	Age (yr)	Heart disease	Class	Digitalis	Arrhythmia	Other complications	Comments
Digitalis Induced Arrhythmias								
W B	1	37	Aortic stenosis and aortic insufficiency	IIB	Digoxin 0 5 mg	Nodal tachycardia and bigeminy	BUN = 26	Cleared with KCl in 24 hr
W B	2	37	Aortic stenosis and aortic insufficiency	IIIC	Gitalin 0 5 mg	A V dissociation and bigeminy	BUN 50	Died with toxicity
E E	1	30	Mitral insufficiency and mitral stenosis	IIIC	Leaf 0 2 Gm	Auricular fibrillation with slow nodal rhythm	BUN = 32	Cleared in 3 days with KCl
E E	2	31	Mitral insufficiency and stenosis	IIIC	Leaf 0 2 Gm	Bigeminy auricular fibrillation	K± 3 2 mEq /L	Cleared in 1 day without KCl
E E	3	32	Mitral stenosis and insufficiency	IVE	Leaf 0 2 Gm	Bigeminy and nodal tachycardia		Cleared in 3 days with KCl
E E	4	34	Mitral stenosis and insufficiency	IVE	Leaf 0 2 Gm	Nodal tachycardia	Normal BUN K± 3 8 mEq /L	Died in intractable failure
R O B	1	35	Aortic stenosis and aortic insufficiency	IIB	Gitalin 0 5 mg	Paroxysmal atrial tachycardia with 2 1 block		Normal sinus rhythm after D/C digitalis
R W	1	32	Mitral stenosis	IIB	Digitoxin 15 mg	Wenckebach phenomenon and A V dissociation		Normal sinus rhythm in 40 hr after D/C digitalis
R W	2	3?	Mitral stenosis	IIB	Digitoxin 0 15 mg	A V dissociation		Normal sinus rhythm in 24 hr after D/C digitalis

lation and other arrhythmias was 15 3 12 5 and 13 1 years respectively

D TYPES OF HEART DISEASE Valvular lesions were divided thus mitral stenosis 14 cases mitral insufficiency 9 cases combined mitral stenosis and insufficiency 5 cases aortic valvular disease 16 cases and combined mitral (tricuspid) and aortic valve disease 8 cases

Table II summarizes the types of rhythms present in association with the various valvular lesions

E THERAPEUTIC AND FUNCTIONAL CLASSIFICATION Table III summarizes the therapeutic and functional classification as related to observed rhythms

F DIGITALIS Eighteen patients (33 admissions) were receiving digitalis

G OTHER CONTRIBUTING FACTORS Four patients demonstrated both clinical and biochemical evidence of hepatic disease Three patients had significant renal disease reflected by persistent albuminuria associated with a blood urea nitrogen in excess of 40 mg per cent These patients with hepatic or renal disease were equally distributed with regard to cardiac rhythm (normal sinus auricular fibrillation and other disorders of the heartbeat) Nine patients (12 admissions) had undergone cardiac surgery Finally there were 7 deaths among the 31 patients studied

Table I. Veterans Administration Hospital. Clinical findings in male patients with rheumatic heart disease—Cont'd

Patient	*Number of admissions*	*Age (yr.)*	*Heart disease*	*Class*	*Digitalis*	*Arrhythmia*	*Other complications*	*Comments*
				Nondigitalis Induced Arrhythmias				
E. K.	1	36	Aortic stenosis and insufficiency. Mitral and tricuspid stenosis	IIIC	Digoxin 0.5 mg.	1° A-V block		Stable P-R interval
E. K.	2	36	Aortic stenosis and insufficiency. Mitral and tricuspid stenosis	IIIC	Leaf 0.1 Gm.	1° A-V block		Stable P-R interval
T. L.	1	40	Aortic stenosis	IIB	Digoxin 0.5 mg.	1° A-V block	( ) Rheumatic carditis	
J. S.	1	[illegible]	Mitral insufficiency	IIIC	0	1° A-V block	Rheumatic fever recurrence	
D. Y.	1	30	Aortic stenosis and insufficiency. Mitral stenosis	IIIC	Leaf 0.1 Gm.	1° A-V block	None	Stable P-R interval

Table II. Veterans Administration Hospital. Rhythm versus valvular lesion in male patients

	Mitral stenosis	*Mitral insufficiency*	*Mitral stenosis and insufficiency*	*Aortic*	*Combined*
Normal sinus rhythm	5	8		12	4
Auricular fibrillation	7		1		1
Arrhythmias	2	1	4	4	3
Digitalis-induced	2		4	3	
Nondigitalis-induced		1		1	3

Table III. Veterans Administration Hospital. Rhythm versus therapeutic and functional classification in male patients

	Class 1A	*Class 1B to 2B*	*Class 3C to 4E*
Normal sinus rhythm	6	12	11
Auricular fibrillation		6	3
Arrhythmias		5	9
Digitalis-induced		4	5
Nondigitalis-induced		1	4

Table I Veterans Administration Hospital Clinical findings in male patients with rheumatic heart disease

Patient	Number of admissions	Age (yr)	Heart disease	Class	Digitalis	Arrhythmia	Other complications	Comments
			Digitalis Induced Arrhythmias					
W B	1	37	Aortic stenosis and aortic insufficiency	IIB	Digoxin 0 5 mg	Nodal tachycardia and bigeminy	BUN = 26	Cleared with KCl in 21 hr
W B	2	37	Aortic stenosis and aortic insufficiency	IIIC	Gitalin 0 5 mg	A V dissociation and bigeminy	BUN = 50	Died with toxicity
E E	1	30	Mitral insufficiency and mitral stenosis	IIIC	Leaf 0 2 Gm	Auricular fibrillation with slow nodal rhythm	BUN = 32	Cleared in 3 days with KCl
E E	2	31	Mitral insufficiency and stenosis	IIIC	Leaf 0 2 Gm	Bigeminy auricular fibrillation	K± 3 2 mEq /L	Cleared in 1 day without KCl
F E	3	32	Mitral stenosis and insufficiency	IVE	Leaf 0 2 Gm	Bigeminy and nodal tachycardia		Cleared in 3 days with KCl
E E	4	34	Mitral stenosis and insufficiency	IVE	Leaf 0 2 Gm	Nodal tachycardia	Normal BUN K± 3 8 mEq /L	Died in intractable failure
R O B	1	35	Aortic stenosis and aortic insufficiency	IIB	Gitalin 0 5 mg	Paroxysmal atrial tachycardia with 2 1 block		Normal sinus rhythm after D/C digitalis
R W	1	32	Mitral stenosis	IIB	Digitoxin 15 mg	Wenckebach phenomenon and A V dissociation		Normal sinus rhythm in 40 hr after D/C digitalis
R W	2	32	Mitral stenosis	IIB	Digitoxin 0 15 mg	A V dissociation		Normal sinus rhythm in 24 hr after D/C digitalis

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Table IV. Jackson Memorial Hospital. Clinical findings in male patients with rheumatic heart disease—Cont'd

Patient	*Number of admissions*	*Age (yr)*	*Heart disease*	*Class*	*Digitalis*	*Arrhythmia*	*Other complications*	*Comments*
N.P.	1	28	Mitral stenosis and aortic insufficiency	IV D	Gitalin 0.5 mg.	Multifocal PVCs	SBE	
N.P.	2	30	Mitral insufficiency, stenosis and aortic insufficiency	IV D	Leaf 0.1 Gm.	Auricular fibrillation bigeminy	Severe CHF	Disappeared after digital D/C and oral potassium
C.S.	1	40	Aortic and mitral insufficiency	IV D	Leaf 0.1 Gm.	PAT with 2:1 block PVCs	Heart failure	
			Nondigitalis Induced Arrhythmias					
E.B.	1	31	Mitral and aortic stenosis. Mitral and aortic insufficiency	II B	None	1° A-V block		
A.C.	1	40	Aortic and mitral stenosis. Mitral insufficiency	III C	None	1° A-V block		
A.C.		40	Aortic and mitral stenosis. Mitral insufficiency	IV F	Gitalin 0.5 mg.	1° A-V block		
A.C.	3	40	Aortic and mitral stenosis. Mitral insufficiency	IV E	Gitalin 0.5 mg.	1° A-V block	Acute carditis	
J.D.	1	15	Mitral insufficiency	III C	None	1° A-V block. Interference dissociation	Acute carditis	
J.F.		35	Mitral stenosis and aortic insufficiency	IV D	Digoxin 0.5 mg.	1° A-V block + PVC	CHF	PVCs disappeared with extra digital
J.F.	4	36	Aortic insufficiency and mitral stenosis	IV D	Digoxin 0.5 mg.	1° A-V block PVCs	CHF	Stable P-R interval
C.H.	1	38	Mitral insufficiency	III C	None	1° A-V block		
C.H.	2	39	Mitral insufficiency	III C	None	1° A-V block	(?) Acute rheumatic fever	
E.K.	1	26	Mitral insufficiency	II B	None	1° A-V block		
E.K.	1	[illegible]	Mitral stenosis, aortic stenosis and tricuspid stenosis	III C	None	1° A-V block		
R.L.R.	1	31	Mitral and aortic insufficiency, mitral stenosis	II B	None	1° A-V block	(?) Acute rheumatic fever	
H.S.	1	13	Mitral insufficiency	II B	None	1° A-V block	(?) Acute rheumatic fever	

II. Jackson Memorial Hospital—Male patients

A. CLASSIFICATION OF PATIENTS AND CARDIAC RHYTHMS. In the 4 year study period there were 57 male patients who fulfilled the previously stated criteria. These accounted for a total of 103 separate admissions, an average of 1.8 admissions per patient. Eleven patients with 16 admissions were observed to have auricular fibrillation. Fifteen patients with 26 admissions were noted to have other disorders of the heartbeat. In 7* patients (13 admissions) digitalis intoxication was responsible for the ectopic rhythm. In the other 9* patients (13 admissions) the arrhythmia was unrelated to the administration of a cardiac glycoside. Table IV outlines the clinical findings in all patients with disturbances in rhythmicity.

B. AGE. The average age of the patients was 32.5 years (range, 14 to 40 years). When related to rhythmicity the average age was 32.1 years for those patients with normal sinus rhythm, 35.1 years for those with auricular fibrillation, and 32.1 years for those with other arrhythmias. Those patients in the latter group with digitalis cardiotoxicity were slightly older (34.6 years) than those whose arrhythmias were unrelated to digitalis (32.8 years).

C. DURATION OF DISEASE. There was no apparent difference in the duration of rheumatic heart disease between the patients with normal sinus rhythm (19.5 years), those with auricular fibrillation (24.2 years), and those with other arrhythmias (20.0 years).

D. TYPES OF HEART DISEASE. There were 21 patients with mitral stenosis, 10 with mitral insufficiency, and 14 with combined mitral lesions. Isolated aortic valvular disease was diagnosed in 16 patients. The other 42 patients manifested combined mitral (tricuspid) and aortic valvular disease. Table V summarizes the mechanism of the heartbeat in patients with different valvular lesions.

E. THERAPEUTIC AND FUNCTIONAL CLASSIFICATION. Table VI shows the relationship of therapeutic and functional class to the observed rhythm.

F. DIGITALIS. Thirty-four patients (69 admissions) received one or more of the various digitalis preparations.

G. OTHER CONTRIBUTING FACTORS. A study was made of the clinical records in 19 instances of valvular surgery; this represented 13 patients (multiple admissions in this group were common). In the case of 11 admissions hepatic disease appeared to be of major clinical significance; in 9 of these, however, the clinical and biochemical derangements were not severe. Impaired liver function was present in 5 patients who developed digitalis cardiotoxicity, but in only one patient was this impairment considered to be severe. Six patients demonstrated significant renal disease. However, 4 of these had a blood urea nitrogen of less than 40 mg. per cent. In the other 2 patients with significant renal impairment, disturbances in cardiac rhythmicity were not observed. There were 8 deaths during this four-year interval among these male patients with rheumatic heart disease.

III. Jackson Memorial Hospital—Female patients

A. CLASSIFICATION OF PATIENTS AND CARDIAC RHYTHMS. During the 4 year study period a total of 95 female patients (ages 14 to 40 years) was noted to have clinical evidence of rheumatic heart disease. These patients represented 151 hospital admissions (1.6 admissions per patient). Twenty-two patients (42 admissions) had auricular fibrillation. Twelve patients (12 admissions) showed other disorders of the heartbeat. In this last group, 6 patients were interpreted as having disturbances in rhythmicity secondary to digitalis. Table VII summarizes the clinical findings in the 12 patients with ectopic rhythms.

B. AGE. The average age of the female patients was 34.7 years. The average age of those who manifested normal sinus rhythm was 30.4 years (range, 16 to 40 years). Those patients with auricular fibrillation averaged 32.1 years (range, 15 to 40 years). The third group was divided into patients with digitalis-induced and nondigitalis-induced arrhythmias, and the average ages were 33.5 and 28.2 years, respectively.

C. DURATION OF DISEASE. The average duration of the rheumatic heart disease

*One patient had disturbances in rhythmicity both related and unrelated to digitalis on separate admissions.

was 18.2, 22.7, and 25 years, respectively, in those with sinus rhythm, those with auricular fibrillation, and those with other arrhythmias.

D. TYPES OF HEART DISEASE. Fifteen patients had mitral insufficiency. There were 57 patients with mitral stenosis, 41 instances of combined mitral valvular disease, 6 patients with aortic valvular disease, and 32 patients who showed combined mitral (tricuspid) and aortic valvular disease. Table VIII presents the mechanism of heart action in patients with different valvular lesions.

E. THERAPEUTIC AND FUNCTIONAL CLASSIFICATION. The relationship between therapeutic and functional classification and rhythm is summarized in Table IX.

F. DIGITALIS. There were 59 individual patients (96 admissions) who were receiving some form of digitalis.

G. CONTRIBUTING FACTORS. There were 32 individual patients (51 separate admissions) who underwent cardiac surgery. Five patients demonstrated hepatic disease and another 5 patients presented clinical evidence of renal impairment. Of these 10 patients, one with disturbance of liver function had an arrhythmia unrelated to digitalis and one with severe renal disease developed clinical and electrocardiographic findings compatible with digitalis intoxication. There were 7 deaths over the 4 year interval in the 95 female patients. This represents an incidence of 7.4 per cent of the total rheumatic heart disease population and 4.6 per cent of female rheumatic heart disease admissions during the study period.

Discussion

With the exception of the ventricular response in auricular flutter and auricular fibrillation, the only consistent determinant for the state of digitalization is the clinical assessment of the patient.

A constellation of factors are involved in determining the adequacy of digitalization. Diminished tolerance to digitalis may be observed in chronic pulmonary disease, renal failure, hepatic decompensation, acute myocardial infarction, and rapid diuresis.[4,18]

Such influences as age and weight of the patient appear to be infrequently considered in determining digitalis dosage. It would appear that the large patient should require more digitalis; it also appears that patients in the older age group

Table V. Jackson Memorial Hospital. Rhythm versus valvular lesion in male patients

	Mitral stenosis	*Mitral insufficiency*	*Mitral stenosis and insufficiency*	*Aortic*	*Combined*
Normal sinus rhythm	11	4	17	16	18
Auricular fibrillation	5	1	2		8
Arrhythmias	5	5			16
Digitalis-induced	5				8
Nondigitalis-induced		3			8

Table VI. Jackson Memorial Hospital. Rhythm versus therapeutic and functional classification in male patients

	Class 1A	*Class 1B to 2B*	*Class 3C to 4E*
Normal sinus rhythm	16	17	28
Auricular fibrillation	—	2	14
Arrhythmias		6	20
Digitalis-induced		2	11
Nondigitalis-induced		4	9

may require somewhat smaller doses of cardiac glycoside.

One of the most readily evaluated factors in determining the patient's tolerance appears to have been neglected in considering digitalis dosage specifically, the patient's sex. Sex has essentially been ignored except when related to the patient's weight, i.e., female patients require less digitalis because of smaller size.

Table XII. Jackson Memorial Hospital. Clinical findings in female patients with rheumatic heart disease

Patient	Number of admissions	Age (yr.)	Heart disease	Class	Digitalis	Arrhythmia	Other complications	Comments
			Digitalis-Induced Arrhythmias					
M. A.	1	34	Mitral and tricuspid stenosis. Tricuspid insufficiency	IIIC	Digitoxin 0.15 mg.	Very slow auricular fibrillation (below 40)	Sudden diuresis	Rate returned to 60 after D/C digitalis in 48 hr.
H. C.	1	37	Mitral stenosis and insufficiency	IIB	Leaf 0.1 Gm.	Multifocal PVCs		PVCs cleared in 48 hr. after digitalis D/C
S. F.	1	39	Mitral stenosis	IIIC	Digitoxin 0.4 mg. daily for 3½ days	Nodal rhythm and bigeminy	On oral estrogen prior to admission	Developed slow idioventricular rhythm prior to death
A. M.	1	25	Aortic insufficiency	IIIC	Digoxin 0.5 mg.	1° A-V block		Developed 1° block after digitalization
A. S.	1	39	Mitral and tricuspid stenosis and insufficiency	IVE	Digoxin 0.25 mg.	Auricular fibrillation with bigeminy	CHF	
H. T.	1	27	Mitral stenosis and mitral insufficiency	IIIC	Digoxin 0.25 mg.	Wandering pacemaker and bigeminy	Recent cardiac surgery	Disappeared after digitalis D/C
			Nondigitalis-Induced Arrhythmias					
M. B.	1	40	Mitral and tricuspid insufficiency. Mitral stenosis	IVE	Digoxin 0.5 mg.	PVCs with rapid auricular fibrillation	CHF	PVCs disappeared with 6 mg. digitoxin and mercurial diuretics
D. H.	1	15	Mitral stenosis	IA	None	1° A-V block		
R. R.	1	20	Mitral insufficiency	IIIC	None	1° A-V block		
V. R.	1	27	Aortic stenosis and aortic insufficiency	IIIC	Gitalin 0.5 mg.	1° A-V block	Admitted for valvular surgery	Stable P-R interval
M. S.	1	37	Mitral stenosis. Mitral and aortic insufficiency	IVE	Digoxin 0.25 mg.	Auricular fibrillation with nodal tachycardia	Massive pulmonary infarct	
L. W.	1	30	Mitral and aortic stenosis. Mitral and aortic insufficiency	IVE	None	Nodal tachycardia	Severe CHF	Terminal event

Recent experimental work has focused on the influence of sex in digitalis tolerance.[3] Grinnell[10,11] and his group have shown that castrated female dogs treated with estrogens are resistant to digoxin cardiotoxicity. The tolerance of untreated castrated female dogs was similar to that of normal male animals. In an extension of their original work, Grinnell and associates[11] demonstrated that a synthetic estrogenic compound, 1, 3, 5 (10), 16-estratetraen-3-01 methyl ether, afforded greatest protection against intoxication with digoxin; this compound curiously failed to demonstrate estrogen effect on vaginal smears.

Recently, in our laboratory, we have confirmed Grinnell's original work utilizing matched pure-bred rabbits. With standard digoxin biotassy, a highly significant increase in the survival time of female rabbits as compared to males was demonstrated. We have also recently observed that marked elevations in the serum cholesterol (a steroid with a chemical configuration similar to estrogen) protect against experimental digitalis intoxication.[12]

In reviewing previously reported cases of digitalis poisoning, it has been difficult to determine whether females show an increased resistance to the cardiotoxic effects of digitalis. This may be due primarily to the advanced age of the patients; most female patients reported have been postmenopausal. In four large series of patients with digitalis intoxication,[13,14] totaling 307 patients, 129 episodes were recorded in females. The age of these patients, however, was for the most part in the fifth decade or above.

In order to assess more precisely the influence of sex on digitalis-induced disorders of the heartbeat, a review of young cardiac patients of both sexes was undertaken. In the present study, 183 patients (306 hospital admissions) were analyzed. The patients consisted of a group of hospitalized young male veterans, a separate group of young males, and a third group derived from a population of young female patients at a university county hospital. The clinical diagnosis in all patients was rheumatic heart disease.

It should be appreciated that any retrospective study has certain inherent weaknesses. This study may be criticized because the diagnosis of rheumatic heart disease in some of the patients was made on a clinical

Table VIII. Jackson Memorial Hospital. Rhythm versus valvular lesion in female patients

	Mitral stenosis	*Mitral insufficiency*	*Mitral stenosis and insufficiency*	*Aortic*	*Combined*
Normal sinus rhythm	41	13	22	4	17
Auricular fibrillation	14	1	17		10
Arrhythmias	2	1	2	2	5
Digitalis-induced	1		2	1	2
Nondigitalis-induced	1	1		1	3

Table IX. Jackson Memorial Hospital. Rhythm versus therapeutic and functional classification in female patients

	Class 1A	*Class 1B–2B*	*Class 3C–4E*
Normal sinus rhythm	19	49	29
Auricular fibrillation		6	36
Arrhythmias	1	1	10
Digitalis-induced		1	5
Nondigitalis-induced	1		3

basis during relatively short periods of hospitalization. In many patients the diagnosis was substantiated by findings at cardiac catheterization and/or operation. It might be said also that it is difficult to record all disorders of the heartbeat which develop in a hospital population attended by a variety of members of the house staff and by other physicians. Finally, observations on the effects of drugs or other etiological considerations in the pathogenesis of ectopic rhythms are, at the best, imperfectly defined.

When only those patients receiving digitalis were compared, 22.2 per cent of the male patients studied at the Veterans Administration Hospital during one or another hospitalization developed signs of *digitalis intoxication. In digitalized* male patients at Jackson Memorial Hospital the incidence was 20.6 per cent. In females at Jackson Memorial Hospital only 10.2 per cent of those receiving digitalis developed digitalis-induced arrhythmias. A statistical analysis was performed comparing the difference in the incidence of digitalis cardiotoxicity in the combined male and female patients. Only those patients who were actually receiving digitalis were included; furthermore, the analysis was based on individual patients and not on total admissions. Utilizing the chi-square test, a p value of between 0.1 and 0.2 was obtained.

These clinical findings support experimental studies which suggest that females have an increased resistance to the cardiotoxic effects of cardiac glycosides. It is important, however, to make certain that these differences occurred in a relatively homogeneous hospital patient population. *If, for example, one* group was composed of pre-terminal patients with severe hepatic and renal disease, and the second group was composed of relatively asymptomatic patients, then any difference in digitalis tolerance might simply reflect a difference in severity of the heart disease.

In many respects the three groups of patients were homogeneous. Similarities include age, average number of admissions per patient, and percentage of patients receiving digitalis.

Certain basic differences were encountered, however. When the duration of known rheumatic heart disease was tabulated, it was observed that both the male and female patients at Jackson Memorial Hospital had their disease an average of 5 to 10 years longer than did the males at the Veterans Administration Hospital. There were fewer deaths among female patients on a percentage basis than in the male population. Also, fewer females presented with coexistent hepatic and renal disease. The distribution of patients in the three groups with regard to their *functional and therapeutic classification* was somewhat different. However, this difference was not marked and does not appear to be related to the reported differences in rhythmicity, since almost 50 per cent of the females were considered to be Class III or worse.

Mitral valve lesions were more common among the female patients.[15] It may be that the higher percentage of aortic and combined valvular lesions in males would predispose to an increased frequency of ectopic rhythms in spite of the similarity of the three groups in their therapeutic and functional classifications.

It might be expected that, because the female patients were somewhat smaller (average weight 126 pounds) than the males (average weight 146 pounds), they would be more prone to develop digitalis cardiotoxicity should they have received a "standard" dose of a glycoside.

It appears, therefore, that in certain vital areas our three groups of patients (two male and one female) have essential differences. These dissimilarities may contribute to the differences in digitalis-induced arrhythmias observed between the sexes. However, the clinical data presented and the increasing experimental evidence of a difference in tolerance to digitalis among the sexes must be considered as an important additional factor in digitalization. Of equal or greater importance, however, is the hope that this study may stimulate new approaches to the study of digitalis and cardiotoxicity.

Summary

The possible difference in digitalis sensitivity between males and females was determined in three groups of young patients with rheumatic heart disease. A

total of 183 patients with 306 separate admissions was studied In the two groups of male patients receiving digitalis 22 2 and 20 6 per cent developed digitalis induced arrhythmias In contrast only 10 2 per cent of the female patients receiving digitalis became toxic Although this difference is not highly significant statistically it is quite suggestive that the female is less sensitive to the cardiotoxic effects of digitalis This would be clinical confirmation of previously reported experimental work showing sex differences in digitalis sensitivity

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Experimental and laboratory reports

The ultrastructural basis of Starling's law of the heart. The role of the sarcomere in determining ventricular size and stroke volume

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The observation that ventricular stroke volume depends on the size of the ventricle prior to the onset of contraction (end-diastolic ventricular volume) comprises one of the fundamental generalities of cardiac physiology. Applying the principle derived from skeletal muscle that increased initial muscle length engenders increased force of contraction, Frank[1] using the frog heart first demonstrated the dependence of stroke volume on initial ventricular volume. These views were further extended and generalized by Starling in the dog. Subsequently, the observations of Frank and Starling have been confirmed in principle and extended to the study of the ventricle in various functional states using atrial and ventricular end-diastolic pressures as an indication of ventricular volume.[3] More recently, by use of indicator dye dilution or angiocardiographic techniques, it has been possible to measure the end-diastolic ventricular volume (EDV) and relate this to ventricular stroke volume (SV).[4-8] From these studies has emerged the fact that not only is stroke volume a function of end-diastolic volume in accord with the Frank-Starling principle, but also that the ratio of stroke volume to end-diastolic volume is relatively constant in a large number of species. Thus Holt[4] has found that the ventricle ejects approximately 43 per cent of its initial volume during contraction in the rat, rabbit, horse, and cow, encompassing a nearly fifty-fold difference in end-diastolic ventricular volumes. For the dog, a SV to EDV ratio of 40 to 45 per cent has been found with a range of 25 to 60 per cent.[4] In man at rest, the SV to EDV ratio also approximates 45 per cent, with a range of 25 to 50 per cent.[9-11] The ratio of SV to EDV, the essential fact of Starling's law, is not constant but may be increased by interventions which enhance contractility, such as sympathomimetics,[8] or decreased when ventricular performance is depressed.[11] Nevertheless, the relative constancy of SV to EDV provides an interesting element

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of order and predictability to the Frank Starling principle for which no ready explanation has thus far been offered

This communication is directed to two closely related questions (1) What is the ultrastructural basis of the Frank Starling law of the heart (2) Are the limits of ventricular end diastolic volume and stroke volume as noted above determined by the fine structure of heart muscle? The answer to both these questions we hope to find in the properties of the sarcomere the ubiquitous structural and functional unit of muscular contraction

Fine structure of heart muscle

Cardiac muscle is composed of branching fibers or cells the lateral boundaries of which are the sarcolemmae and the longitudinal limits the intercalated discs These fibers in turn contain multiple myofibrils running in parallel the length of the cell The myofibrils contain the contractile substance of the muscle and are composed of repeating units termed *sarcomeres* The sarcomeres the primary units of contraction which are arranged in series along the myofibril[1 13] have a distinctive detailed structure which is best perceived with the electron microscope Sarcomeres are bounded longitudinally by a pair of dark lines the Z lines and measure 1 5 to 2 5 microns in length As illustrated in Fig 1 the band like appearance of the sarcomere results from the disposition of two sets of contractile filaments which are arranged in a partially overlapping interdigitating array Thicker filaments presumably composed of myosin and fixed in length extend throughout and are confined exclusively to the central dark A band (see Fig 1) Thinner filaments presumably actin extend from the Z line through the I and A bands and end at the edge of a central lighter area in the A band termed the *H zone*[1] Thus actin and myosin filaments overlap only in the A band exclusive of the H zone The fact that the bands of the sarcomere reflect the contractile filament disposition was initially demonstrated in skeletal and subsequently affirmed as well for heart muscle[13] This structural arrangement and the knowledge that actin and myosin along with calcium and a high energy source (ATP) are somehow involved in the contractile process[14] has formed the basis of most current theories of muscle contraction[1 15]

Ultrastructural basis of Starling's law of the heart

In order to explore the ultrastructural basis of the increase in force of contraction engendered by an increase in muscle length the papillary muscle preparation of the cat has been used Some details of this preparation and its electron microscopic analysis have been presented elsewhere[6] These studies have shown that within the physiologic limits of the length tension curve of heart muscle wherein an increase in muscle length brings about an increase in actively developed force of contraction sarcomere length (Z to Z measurement) is a direct function of muscle length[16] Since force of contraction is also a function of initial muscle length the muscle length tension curve which is the mechanical basis of the Frank Starling principle may be expressed as a *sarcomere length tension curve* Such a relation is portrayed in Fig *2A* This sarcomere length tension curve provides an ultrastructural basis for Starling's law of the heart On this basis Starling's law of the heart can be restated in ultrastructural terms The force of contraction of cardiac muscle is a function of muscle sarcomere length prior to the onset of contraction Of course given an initial sarcomere length as determined by muscle length cardiac muscle contraction is also dependent on the functional state of the muscle as well as determined by such conditions as frequency of contraction and chemical environment[7]

Structurally the relation of sarcomere length to muscle length may be further refined The increase in sarcomere length which accompanies an increase in cardiac muscle length occurs by an increase in the width of the sarcomere I bands without perceptible change in the A band or H zone (Figs *3A* and *3B*) These sarcomere bands are of interest since they reflect the disposition of underlying myofilaments The motion of thin (actin) filaments relative to thick (myosin) filaments in the A band forms the basis of the now well supported sliding model for muscle contraction[1] Although the contractile filaments

of both heart and skeletal muscle have similar dimensions and in general the underlying contractile processes are in all likelihood the same certain functional questions about the purely sliding mechanism have been raised[16] Thin actin filaments *measure 1 0 μ from the Z line to the edge* of the H zone Thus in sarcomeres less than 2 0 μ in length which are found on the ascending limb of the length tension curve sliding actin filaments must meet in the center of the sarcomere and either fold or bypass each other thus creating a double overlap of thin filaments in the center of the A band Although previous observations tended to favor the former possibility[18] more recent work[18,19] would lend support to the view that in both skeletal and heart muscle thin filaments may indeed remain constant in length during sliding at short sarcomere lengths and penetrate the center of the sarcomere The crux of this latter argument lies in the fact that at shorter sarcomere lengths the light area at the center of the A band (termed the *H zone* but more properly called the *L line–M line complex*) does not exclude the presence of actin filaments[19] Furthermore with sarcomere lengths of 1 8 μ or less a secondary contraction band pattern is observed in the center of the A band possibly reflecting a double overlap of thin filaments tra

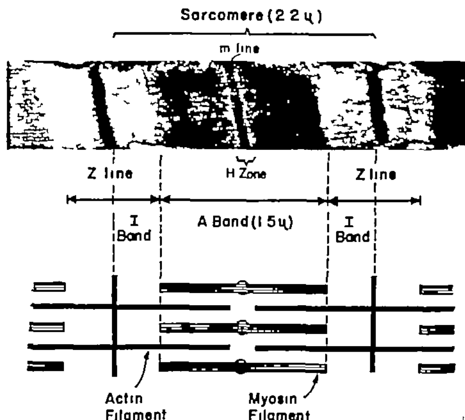


Fig 1 *Above* A typical sarcomere as seen with the electron microscope The dark central A band may be noted flanked by the lighter *I* bands which in turn are transected by the *Z* lines The center of the *A* band reveals a lighter area which may be termed the *H* zone *Below* In schematic form the disposition of the contractile filaments actin and myosin is shown relative to the bands of the upper sarcomere The partial overlapping array of these filaments results in the band pattern as seen above The light areas flanking the dark *m line* at the center of the sarcomere may not be a true H zone at sarcomere lengths of 2 2 μ or less since this area may reflect differences in the density of the myosin filaments rather than the disposition of actin filaments For the sake of simplicity however this area has been called an H zone in the present discussion

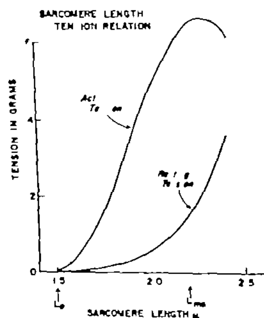


Fig. 2A. Sarcomere length-tension relation. Isometric tension has been expressed as a function of sarcomere length. This relation was obtained by fixing cat papillary muscles at various points along previously determined length-tension curve.[16] Initially sarcomere length was shown to be a direct function of resting muscle length. This has made possible the present plot of tension as a function of sarcomere length. Note that at the point at which both resting and actively developed tension approach zero (L_o) the sarcomere length is 1.5 μ. When initial muscle length is increased until actively developed tension reaches a maximum (L_{max}), an increase over L_o which averages 45 per cent, sarcomere length is increased to 2.2 μ. Note also that resting tension has increased considerably by increasing muscle length from L_o to L_{max}.

versing the sarcomere center. The sliding model for contraction[1,11] would thus appear to be consonant with sarcomere band patterns along the ascending portion of the length-tension curve as well as the descending limb of the curve from which it was originally described.

Although still a matter for active study, the decrease in active tension observed as heart muscle shortens along the ascending limb of the length-tension curve might be explained either by a steric interference of a double overlap of thin myofilaments or by a decrease in the interaction of thick and thin filaments as the interfilamentous spacings enlarge at smaller sarcomere lengths. The force of myocardial contraction then depends not only on sarcomere length prior to contraction but also on the disposition of actin filaments relative to fixed myosin filaments.

Sarcomere structure as determinant of cardiac output

An analysis of sarcomere changes relative to changes in muscle length offers insight into the limits of myocardial performance, since ultimately the activity of the muscle is only a reflection of summated sarcomere performances. Returning to Fig. 2A, one may note that at the point along the active length-tension curve of heart muscle at which actively developed tension is maxi-

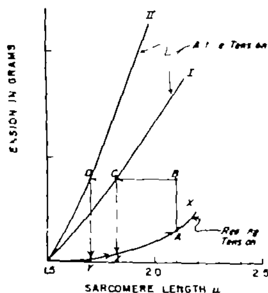


Fig. 2B. Sarcomere shortening under afterloaded conditions. Hypothetical curves for the cat papillary muscle drawn within limits of experimental data. On the abscissa is sarcomere length, the ordinate is tension. Curve I represents the active tension curve of a relatively depressed muscle, whereas Curve II represents a muscle whose contractility has been augmented. If an afterloaded muscle starts contracting at A on the resting curve with an afterload of X, it will first develop force without a change in overall length to match X (A to B) and then shorten until it reaches the active tension curve (B to C). The muscle then relaxes (C to Z) and is brought back to its initial length (A on the resting curve) by a small load termed the *preload*. In this instance in which contractility may be said to be depressed, sarcomere shortening is 15 per cent (2.1 to 1.8 μ). If the muscle were to shorten to Curve II (i.e., B to D), sarcomere shortening is increased to 20 per cent. Hence under afterloaded conditions sarcomere shortening ranges between 15 and 20 per cent of initial length.

mal sarcomere length is 2 2 μ This muscle length has been termed L With a 30 per cent decrease in muscle length actively developed tension falls to zero while sarcomere length decreases to 1 5 μ We have termed this point of the curve I The lower limits of this curve are imposed by the structure of the sarcomere At a sarcomere length of 1 5 μ the Z lines the longitudinal boundaries of the sarcomere abut on the A band The A band which forms a fixed central zone of the sarcomere *remains constant in length* The *functional* upper limit of this curve would appear to be fixed by the precipitous rise in the resting tension of the muscle From this information it is evident that were heart muscle to shorten from the outside limits of the ascending portion of the length tension curve (i e from 2 2 to 1 5 μ) it could shorten approximately 30 per cent of its initial length However this extent of shortening would not appear to occur physiologically Contracting under afterloaded isotonic conditions the muscle will shorten within the limits of the resting and active length tension curves starting on the resting curve developing force to match its imposed afterload and then shortening with this load until the active tension curve is reached (Fig 2B) Thus the muscle does not operate from the extreme limits of its length tension curve As in Fig 2 the course of muscle shortening is determined by its initial length as established by a small resting force (preload) its imposed afterload i e the load it lifts and the given *slope* of the active tension curve The slope of this curve in turn is determined by the functional state of the muscle e g increased by interventions such as norepinephrine[22] If it is assumed that heart muscle were to operate under afterloaded conditions as in Fig 2B the sarcomere would shorten from 2 1 to 1 7 μ This in turn would result in a muscle shortening of only 19 per cent A sarcomere shortening of approximately 15 to 20 per cent may thus be envisioned for isolated heart muscle shortening under physiologic afterloaded conditions

The intact ventricle may also be considered as operating under afterloaded conditions[1] Its initial fiber length is established by a small force the end diastolic ventricular pressure this is analogous to the preload in isolated muscle terms The aortic pressure is the force which the ventricle must overcome in order to eject a volume of blood this is grossly analogous to an afterload since the ventricle only encounters this force with contraction The question can then be asked whether an approximate 20 per cent muscle shortening arrived at from the ultrastructural considerations of the papillary muscle contracting under afterloaded conditions could account for known left ventricular stroke volume

For an initial example let us examine the limits of left ventricular performance in the cat If we consider the ventricle to be a thin walled elastic sphere an admitted oversimplification it is possible to calculate the per cent change in circumference for a given change in volume * The circumferences of the ventricle for given end diastolic and end systolic volumes (EDV and ESV) may then be compared The difference between the two represents the change in circumference of the wall for a given stroke volume (SV = EDV − ESV) Since the ventricular wall is composed essentially of a ring of sarcomeres a given percentage change in circumference may reasonably be taken to represent a corresponding change in sarcomere length In this manner the per cent change in circumferential fiber length has been plotted as a function of end diastolic ventricular volume Fig 4 shows this relation for a range of stroke volumes encompassing those observed experimentally in the open chest cat [1]

From a consideration of Fig 4 in terms of defined ventricular performance several interesting relations emerge First it should be recalled that in accord with the observations of Frank and Starling[1] stroke volume is a function of the end-diastolic volume of the left ventricle for a given functional state of the ventricle The left ventricular end diastolic volume in turn is a function of ventricular end diastolic

* V[illegible] = 4/3 [illegible] (C) = 2πr Then [illegible] C = 2 [illegible]

[illegible] (C) = $\frac{C \quad - C}{C}$ × 100

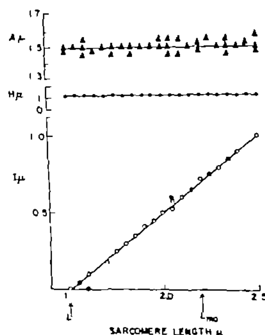


Fig. 31 The relation of sarcomere band to sarcomere length. Values derived from 19 cat papillary muscles fixed at rest at multiple points along the length tension curve. It is noted that with an increase in sarcomere length an increase in the *I* band is observed without perceptible change in either the *A* band or *H* zone. Similar data have also been obtained with human ventricular muscle obtained at the time of corrective surgery (unpublished data).

pressure (LVED) and ventricular distensibility. In order to provide a stroke volume of 2.0 c.c. in the cat that weighs about 2 kilograms, a left ventricular filling pressure of approximately 10 to 12 mm. Hg is required.[1] From recent studies of the resting pressure volume curves of the cat left ventricle we have found that this filling pressure corresponds to a left ventricular volume of 3.5 to 4.0 c.c. If we then apply these values to Fig. 4 and note the point at which the stroke volume curve for 2.0 c.c. intersects with an end-diastolic volume of 4.0 c.c., we find that a circumferential fiber shortening of approximately 20 per cent is required.

Can this analysis be applied to larger mammals? The data in Figs. 5 and 6 would indicate that the same relations hold for the dog and man as for the cat. In both Figs. 5 and 6 the percentage decrease in circumferential fiber length required to eject a given stroke volume has been expressed as a function of end-diastolic ventricular volume. The stroke volumes have been selected to encompass the normal ranges in the dog and man.[3] For a dog of 15 to 20 kilograms, end-diastolic volumes of 35 to 45 c.c. have been observed in the range of normal ventricular function[3,4] (unpublished observations). Given a stroke volume of 15 to 20 c.c. (normal range 16.5 to 20.5 c.c.),[3] we find that a 15 to 20 per cent circumferential fiber shortening is required to accommodate these values. When further applied to man, as in Fig. 6, we also find that the same relation holds and that 15 to 20 per cent fiber shortening is required to eject the normal human stroke volume of 60 to 90 c.c. from an end-diastolic volume of 120 to 180 c.c. The 40 to 50 per cent ventricular ejection (SV = 40 to 50 per cent EDV) observed for man[9,11] is readily accounted for within this value. Furthermore, when the relative movement of superficial fibers of the human ventricular wall has been studied, a 15 per cent muscle shortening has been found, a value which fits well with the foregoing analysis.[20] Thus a 15 to 20 per cent circumferential fiber shortening accounts for the required stroke volumes over a nearly hundred-fold range of end-diastolic ventricular volumes.

A unifying principle evolves from these considerations when sarcomere shortening is considered in terms of the relation of stroke volume to end-diastolic volume. In Fig. 7 we have plotted the per cent decrease in circumference as a function of the ratio of stroke volume to end-diastolic volume. This provides a general relation independent of absolute volumes. One may note that the 43 per cent figure for ventricular emptying derived by Holt for a broad range of animals corresponds to roughly an 18 per cent sarcomere shortening. The literature suggests that the left ventricle normally ejects a stroke volume which is 35 to 50 per cent of end-diastolic volume.[1] Fig. 7 indicates that this requires sarcomere shortening of 15 to 20 per cent. This observation takes on added interest when we recall that this 20 per cent figure is what one might have predicted from an analysis of the sarcomere length tension curve (Fig. 2), assuming that this curve was similar for this entire

range of animals and that the ventricle were to perform along the most efficient portion of the curve. The fact that the residual or end-systolic volume in the heart approximates 50 per cent of the end-diastolic volume then becomes quite reasonable when considered in terms of sarcomere structure and its limits. We have found that structurally there are no distinguishing characteristics between different mammalian hearts, including that of the rat, guinea pig, rabbit, cat, dog, and man; *the sarcomere remains the same in detail and dimensions throughout.*[4] The character of the sarcomere thus governs the requirements of ventricular volume needed to produce a given stroke volume. This relation is clear even when considered in terms of the geometric oversimplifications that we have admittedly made.

The observations of Hort[37] and Linzbach[3] with light microscopy also suggest that the range of sarcomere changes in the ventricle is within limits of 2.0 and 1.4 μ. However, an inability to relate their findings directly to physiologic function as provided by length-tension and pressure-volume curves and an inherent lack of precision due to the limits of light microscopy have left some of their conclusions *previously unsupported.*

Certain other relations deserve mention when ventricular performance is expressed as it is in Figs. 4-6. It is evident that the amount of circumferential shortening required for a given stroke volume de-

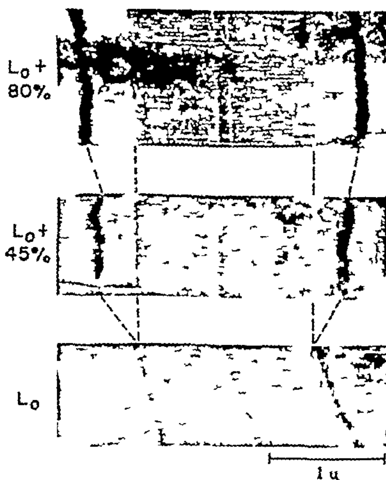


Fig. 3B. The effect of increasing initial muscle length on sarcomere structure. From below upward increasing muscle length (L_0 + increment) produces an increase in the I band with no change in the central A band. L_0 + 45 per cent represents the apex of the length-tension curve or L_{max}.

creases as the end diastolic volume of the heart increases This has been elaborated on previously by Rushmer[23] The apparent initial advantage offered to the ventricle by the lesser circumferential shortening that is necessary at a larger initial ventricular volume for a given stroke volume is mitigated to a great extent by the mechanical disadvantage imposed on the ventricle by the Laplace relation[24,25] According to the Laplace relation a larger intramyocardial force is required to maintain a given intraventricular pressure at a larger initial ventricular volume than at a smaller one Thus the fibers of the larger ventricle have to shorten relatively less than those of the smaller one for a given stroke volume but with a higher intramyocardial force for the same pressure*

Pressure volume sarcomere relations in pathologic states

As emphasized the initial volume of the ventricle is of prime importance for determining stroke volume In the establishment of this initial volume ventricular diastolic distensibility becomes a central concern For a broad range of animals (cat to man) it is interesting that a ventricular filling pressure of approximately 10 mm Hg results in an end diastolic volume which provides for a normal to high stroke volume[2,4] Normally ventricular distensibility is independent of physiologic interventions such as sympathetic stimulation[3] However any marked alteration in the static pressure volume relations of the ventricle (diastolic compliance) could alter ventricular performance significantly at a specified diastolic pressure In this regard Braunwald and Ross[26] have pointed out recently that such changes in diastolic compliance may indeed occur under pathologic conditions For example in the ventricular hypertrophy of aortic stenosis or hypertension intraventricular volume may be small whereas in chronically overdistended hearts (e g mitral insufficiency) intraventricular volume may be quite large for a relatively normal left ventricular end diastolic pressure (LVEDP)[3] The latter pathologic relation is as yet unexplained but may be the end result of the phenomenon of stress relaxation in which after a deformation (stress) of an elastic body a slow decline in the resultant tension (strain) is observed with time An ultrastructural correlate of this phenomenon may reside in the fact that when heart muscle is passively stretched beyond the apex of its active length tension curve (L_{max}) increments in sarcomere length no longer remain entirely proportional to increases in muscle

*The [illegible] myocardial force [illegible] the [illegible] force (F_t) [illegible] ($F = P A$) [illegible] the heart [illegible] The [illegible] (F) [illegible] transected after [illegible] the transect [illegible] pressure (P [illegible] P) [illegible] The [illegible] (F) [illegible] by [illegible] $F = \frac{1}{}$ [illegible] per unit [illegible] (F) [illegible] correct for [illegible] Laplace [illegible] $F = \frac{P}{2}$

Fig 4 The relation of per cent decrease in mean ventricular circumference as a function of end diastolic ventricular volume has been derived for a range of stroke volumes which encompass those attained by the cat left ventricle An average normal stroke volume for the cat approximates 2 cc when a filling pressure of 12 mm H_2O which thus would require would correlate with an end diastolic volume of 4 cc as determined from static pressure volume curves (unpublished observations)

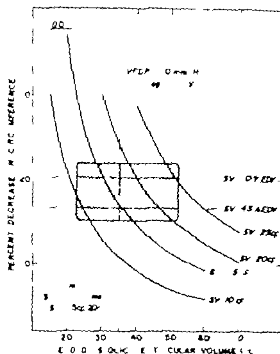


Fig 3 F the dog (15 Kg) the rel tion of de rease in entricular cir umference to end-diastolic ve tri ula volume is illustrated Three t oke volume (SV) have been selected a in Fig 4 to enc mp the range of normal dog stroke ol ume The ertic l dashed line represents the end dia t lic lume which correspond to a left ven tri ular filling pressure of 10 mm Hg (unpublished observ tions) The horizontal dashed lines represent two entricular ejection states when SV = 43 per cent of end-diastolic olume (*EDV*) as given by Holt and SV = 50 per cent of EDV Note that a 16 to 20 per ent circumferential fiber shortening would encompass the intersection of this data

length.[16, 7] This suggests that some slippage of muscle cells relative to one another occurs in chronic ventricular overdistention The anticipation that overstretched heart muscle would result in the ready disengagement of thick and thin filaments in the A band as would be inferred from simple analogy with skeletal muscle[11, 22] has not been borne out in the myocardium.[18, 4] Thus by itself filament disengagement cannot explain myocardial failure However in ventricles passively filled to pressures of 30 to 35 mm Hg which is well above physiologic limits a true enlarging H zone may be seen (unpublished observations) attesting to the fact that filament disengagement may also ultimately ensue with marked dilatation of the ventricle Two direct factors may thus be involved

in the decompensation of the dilated ventricle First a relative slippage of muscle fibers in the chronically overdistended failing heart would result in relatively shorter sarcomeres than would be anticipated from the over all degree of ventricular distention This view has been suggested by Hort[7] and Linzbach[8] on the basis of light microscopy and it is supported now with electron microscopy Slippage of heart muscle fiber would also help to explain the normal left atrial pressures that are observed occasionally in the markedly overdistended atria of mitral insufficiency.[14] And second some degree of filament disengagement may also occur

In contrast to the overdistended ventricle the occurrence of short sarcomeres with a small mitral ventricular volume and elevated ventricular filling pressure may be inferred in pulsus alternans wherein inadequate muscle relaxation has been shown to occur prior to the alternating weaker ventricular contraction.[15] In this situation the sarcomeres start to contract before being completely

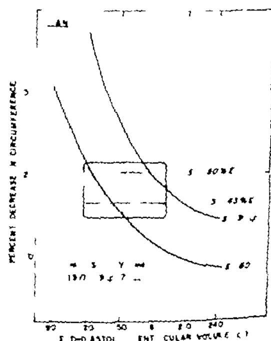


Fig 6 \ in Fig 4 and 5 the pe t d re e in left v nt ular circumference h been g en function of end-di t lic left ventricular olume f m n Stroke volume (SV) curve an g en t encompa the range of n rmal t ke volum man See text

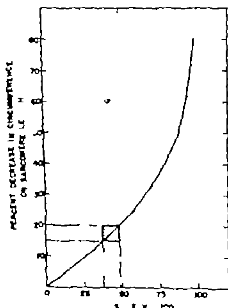


Fig. 7. Per cent decrease in circumferential fiber length or sarcomere length expressed as a function of the ratio of stroke volume (SV) to end-diastolic volume (EDV). The normal limit of sarcomere shortening, are 15 to 20 per cent, corresponding to SV/EDV of 38 to 49 per cent (*shaded area*).

relaxed from a prior contraction. The result is the same as if the muscle were to shorten from a shorter effective length. A less forceful contraction ensues. Thus the relation of sarcomere length to end-diastolic pressure and volume is of some importance in the defining of disordered function. The exact definition of these interrelations under more specific conditions will require further study.

Summary

The relation of the ultrastructure of heart muscle to ventricular function has been discussed. The fact that the length of the sarcomere, the unbiquitous unit of contraction, is a function of muscle length allows the formulation of a sarcomere length tension curve. This forms the ultrastructural basis of Starling's law of the heart. The limits of sarcomere shortening are discussed (2.2 to 1.5 μ) and the normal range of contraction under afterloaded conditions has been delimited (2.1 to 1.7 μ), thus allowing for a 20 per cent sarcomere shortening. It has been shown that this 20 per cent sarcomere shortening accounts for the ventricular muscle shortening necessary to explain known ventricular performance in the cat, dog and man. On this basis it has been suggested that the initial size of the ventricle required to produce a given stroke volume depends on the structural and functional limits of the sarcomere.

The encouragement and critical advice of Dr Eugene Braunwald is gratefully acknowledged.

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Electrocardiographic changes due to delayed activation of the wall of the right ventricle

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There have been numerous studies of experimental right bundle branch block (RBBB) in man,[1] dogs,[2-6] and cattle.[7,8] In some of these studies, RBBB was induced by damaging or cutting the right bundle branch (RBB) without direct visualization during cardiac catheterization[1] or through atrial[1] or ventricular stab wounds[4]; others observed the conduction system in the open right ventricle during cardiopulmonary bypass.[8] These investigations have dealt primarily with *complete* RBBB which resulted from functional or anatomic interruption of the RBB on the right septal surface.

RBBB in older people often is associated with anatomic lesions of the septal RBB.[9-11] However, the frequent occurrence of partial RBBB in cases of congenital heart disease and its disappearance after corrective surgery[1] suggests that in many cases anatomic lesions of the main right bundle branch may be absent and that the observed electrocardiographic changes may result from involvement of a more peripheral part of the right bundle.[12-14] Cabrera and Monroy[12] showed that in cases of atrial septal defect, tricuspid insufficiency, ventricular septal defect, or arteriovenous shunt, a diastolic overloading of the right ventricle occurs. Several hypotheses have been presented to explain the electrocardiographic evidence of partial or, in some cases, complete RBBB in these conditions. Explanations of the mechanisms involved include the following: (1) an increase in length of the conduction pathway,[13] (2) a decreased density of the junctions between Purkinje fibers and ventricular muscle,[8] or (3) a decreased diameter of the conduction cells which results from stretch of the right ventricle.[7]

It appeared to us that a likely cause of delayed activation of right ventricular muscle in diastolic overload of the right

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ventricle was stretch of the peripheral specialized conducting fibers. This stretch would involve particularly that part of the right bundle which traverses the right ventricular cavity as the moderator band in man or as free running false tendons in the dog. In the latter, this part of the right bundle crosses from the base of the anterior papillary muscle on the right septal surface to the free wall of the right ventricle. During distention of the ventricle, this band of conduction tissue would be most subject to stretch.

The effects on the electrocardiogram of sectioning or stretching the more peripheral parts of the right bundle branch have not been studied extensively. Uhley and Rivkin[8] have made the most systematic study of this sort. However, their experiments were made during cardiopulmonary bypass and required ventriculotomy. Since changes in the QRS complex may follow right ventriculotomy, it seemed to be worth while to conduct further investigations. A technique was developed to study systematically the effects of sectioning different parts of the right bundle branch through a right atriotomy incision during occlusion of venous inflow. Such a technique avoids the electrocardiographic changes which might be produced by ventriculotomy and/or cardiopulmonary bypass. This paper presents the effects on the sequence of right ventricular epicardial activation of sectioning peripheral parts of the canine right bundle branch as well as the chronic effects of this procedure on the electrocardiogram and vectorcardiogram. These changes are contrasted with those which occur after surgical transection of the right main bundle.

Methods

Experiments on isolated tissues. The right bundle branch and surrounding septal ventricular muscle were isolated from dogs anesthetized with sodium pentobarbital (30 mg. per kilogram intravenously). The preparation included that part of the right bundle branch extending from below the bundle of His to just above the anterior papillary muscle. The tissues were perfused with a modified Tyrode solution at 37°C.[1] Ling-Gerard microelectrodes were used to impale single fibers in the right bundle and septal muscle. Transmembrane potentials were recorded through these electrodes using a cathode follower, cathode-ray oscilloscope, and camera; these methods have been described in detail.[1] Rectangular cathodal stimuli from a Tektronix pulse generator and isolation unit were used for intracellular stimulation through another microelectrode.

Acute experiments. Dogs were maintained on cardiopulmonary bypass by methods described previously, and a right ventriculotomy was made. Acrylic plaque electrodes were sutured to the right atrium over the bundle of His, right bundle branch, and to the right and left ventricles. Electrocardiograms and bipolar electrograms from the above-mentioned electrodes were photographed at a paper speed of 200 mm. per second using the Electronics for Medicine oscilloscope. An exploring electrode was used to record the activation time of different areas of the right ventricular epicardial surface before and after stretching of the Purkinje fibers in the free running false tendon (see next section).

Chronic experiments. Eight mongrel dogs which weighed between 18 and 26 kilograms were anesthetized with Pentothal sodium and ventilated by a Jefferson artificial respirator. The Lead II ECG, rectal temperature, and femoral blood pressure were monitored simultaneously on a cathode-ray oscilloscope during the surgical procedures. The heart was exposed through a right thoracotomy. An electrode consisting of 5 silver wires 0.08 inch in diameter embedded in an acrylic plaque was sutured to the epicardial surface of the left ventricle. Activity recorded through this electrode provided a time reference for ventricular activation; this reference was not influenced by minor changes in the position of the heart which occurred during the mapping procedures. The time of activation of 20 to 30 representative right ventricular epicardial sites was determined by use of a bipolar exploring electrode.[n] Bipolar electrograms were recorded simultaneously from the left ventricle and from the different regions of the right ventricle on an 8-channel switched-beam cathode

ray oscilloscope (Electronics for Medicine) at a paper speed of 200 mm per second. Local activation time was measured at the intrinsic deflection of the electrogram. Difference in activation time of the 2 electrograms (left ventricular minus right ventricular) was determined by a precision measuring device which enabled differences of 1 msec to be measured reproducibly. The activation time of each epicardial area was plotted on a map of the right ventricle. This map presented the time sequence of activation of the epicardial surface of the free wall. After the normal heart had been mapped, tapes were placed around the cephalic and caudal venae cavae and the azygos vein was ligated. Occlusion of venous inflow was achieved by tightening the tapes. The free running Purkinje strands in the right ventricle were then sectioned under direct vision through a right atriotomy. Several periods of occlusion of venous inflow, each lasting 2 minutes, usually were required to ascertain the completeness of the sectioning. In one animal the right bundle branch was sectioned at the level of the papillary muscle of the conus. After repair of the atriotomy, activation time at each of the same right ventricular epicardial sites was determined.

Standard bipolar and unipolar limb leads and 4 thoracic electrocardiograms (unipolar V leads) were recorded prior to operation and again at 1, 2, and 3 weeks postoperatively. The thoracic lead positions employed in this study are those of Lannek,[8] plus one additional electrode position at the dorsal spine of the seventh thoracic vertebra (V_{10}). The locations of these lead positions on the thorax are shown in Figs. 5 and 9. CV_6RL is located on the fifth right intercostal space at the sternal border and corresponds roughly to Lead V_1 in man. Lead CV_6LL is placed in the sixth left intercostal space at the sternal border and roughly corresponds to Lead V_2. CV_6LU is in the sixth left intercostal space at the costochondral junction and is equivalent to Lead V_4 in man. Vectorcardiograms (VCGs) were recorded at the same time on 3 of the dogs using the Wilson equilateral tetrahedron and McFee[*] lead systems. Dorsoventral and lateral radiographs were taken preoperatively and postoperatively to demonstrate any change in the position of the heart which might have occurred as a result of the surgical procedure. In all animals the anatomic position of the heart was not altered.

All animals were sacrificed by intravenous injection of pentobarbital sodium and the hearts were studied to determine the nature and extent of the anatomic lesions.

Results

The results reported in Sections A and B are included only to support the interpretations made from studies of chronic preparations.

A. Isolated tissues. Microelectrodes were used to determine whether the right ventricular septum above the anterior papillary muscle can be activated directly from the adjacent right bundle branch (RBB). An isolated perfused preparation was used and two intracellular microelectrodes were placed in fibers of the right bundle branch and one microelectrode was inserted into a septal muscle fiber. One of the intracellular electrodes in the RBB was used to deliver stimuli; the other two electrodes recorded the transmembrane potentials of the RBB and adjacent septal muscle, respectively.

It was found that when a single fiber of the RBB was stimulated through the intracellular electrode the entire RBB was excited. This was shown by action potentials recorded through the other electrode. However, the adjacent septal muscle was not activated. Similar results were obtained when stimulating and recording intracellular electrodes were inserted into the septal muscle and the third microelectrode into a single fiber of the RBB. Propagated activity in the septal muscle failed to excite the right bundle branch.

In Fig. 1,A extracellular electrodes were used to stimulate both RBB and septal muscle simultaneously; activity of the RBB is shown in the middle tracing and that of the ventricular fiber in the lower tracing. These records show that both tissues were electrically excitable and had a normal resting and action potentials.

[*] Constructed by W. Nadas Dennis, Medical Center, Brooklyn, N. Y.

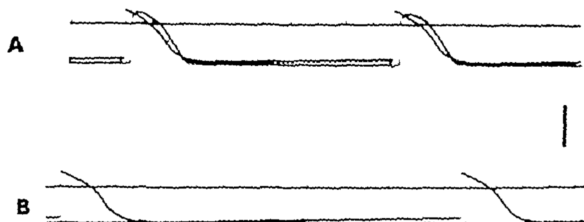


Fig 1 A Simultaneous transmembrane action potentials recorded from a fiber in the right bundle branch (*middle tracing*) and a fiber in the adjoining ventricular septal muscle (*bottom tracing*). The top tracing shows time lines at intervals of 10 and 100 msec The preparation was driven by bipolar electrical stimuli applied to both the right bundle branch and ventricular muscle *B* Recording made from the same two fibers as in A Spontaneous activity in the right bundle branch did not excite the ventricular muscle as evidenced by the absence of change in the resting membrane potential of the ventricular muscle fiber The vertical bar between A and B denotes 100 millivolts

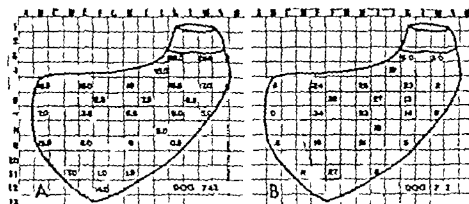


Fig 1 B A Normal right ventricular activation is arbitrarily divided into three areas The anterior septal region is activated first (*clear area*) the mid region next (*dark stippled area*) and the posteroseptal and pulmonary conus regions last (*light stippled area*) Numbers in the respective RV epicardial areas denote time of onset of activation after initial RV activation (in milliseconds) Total activation time in this dog was 28 5 msec *B* The amount of delay and the area of greatest delay (*stippled region*) are shown after sectioning of the free running branches of the right bundle in the same dog

cause of differences in conduction velocity the upstrokes of the two action potentials are not simultaneous In Fig 1 *B* stimulation was stopped The same fiber of the RBB developed spontaneous activity as shown by the slow diastolic depolarization Propagation of this activity to the adjacent ventricular muscle did not occur This is demonstrated by the record on the lower tracing which shows a normal resting potential and complete absence of action potentials in the septal muscle fibers

Therefore interruption of the RBB above the anterior papillary muscle ordinarily would be expected to result in complete right bundle branch block (RBBB) However it has been shown that at or below the level of the anterior papillary muscle the RBB does indeed excite adjacent ventricular muscle cells[11] Thu

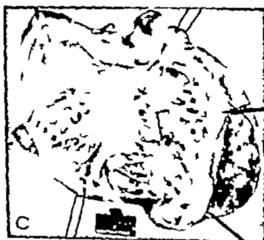


Fig 2C Opened right ventricle of dog in which false tendon was cut Note complete sectioning of main free-running false tendon which extended from the anterior papillary muscle (*right arrow*) to the free right ventricular wall (*left arrow*) also note absence of injury to endocardium

damage to part of the right ventricular specialized conducting tissue at or distal to the anterior papillary muscle would not be expected to result in complete RBBB but rather in some degree of incomplete block or in local delay of ventricular activation

B Acute preparations In dogs studied during cardiopulmonary bypass with right ventriculotomy it was found that progressive stretching of the free running Purkinje fibers resulted in a gradual increase in conduction time from the RBB to the right ventricular epicardium Further stretching completely blocked conduction over this part of the Purkinje system and resulted in considerable delay of activation of the free right ventricular wall However in these studies conduction disturbances may have been a result of the experimental procedure itself i e cardiopulmonary bypass with an opened right ventricular cavity It is difficult to interpret small changes in the time of activation of numerous discrete sites on the right ventricular epicardium in the presence of a right ventriculotomy [18] Also the exact interpretation of changes in limb lead electrocardiograms is subject to error because of the thoracotomy and ventriculotomy

C Chronic experiments A representative map of the normal sequence of activation of the right ventricular epicardium is shown in Fig 2A The numbers in the respective areas represent the time of epicardial activation in milliseconds with zero time as the point of earliest activation For example area B9 was activated 15 msec after area H9 (area H9 is the site of earliest activation) The onset of activity in different gross regions of the epicardium has been divided arbitrarily into three periods The region of earliest activity in all dogs was at the anterior septal margin of the right ventricular epicardium The mid portions of the right ventricle were activated next and the posterior septal margin and pulmonary conus regions were activated last Total right ventricular epicardial activation time varied from 21 to 29 5 msec These results agree with

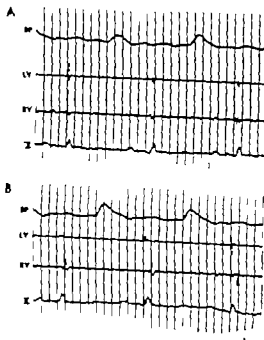


Fig 3 Blood pressure tracing and electrograms recorded from LV a bipolar electrode sewed on the left ventricular epicardial surface RV a roving bipolar electrode placed at the middle of the right ventricular epicardium in an area designated as H5 on the map in Fig 2 and II a Lead II electrocardiogram Time lines are at intervals of 40 msec Recordings in A were made during normal right ventricular epicardial activation and in B from the same dog after complete sectioning of the peripheral free running branches of the RBB Note that prior to sectioning activity at the roving LV electrode precedes that at the reference LV electrode After sectioning (B) RV activity is delayed until after LV activation Dog No 1645

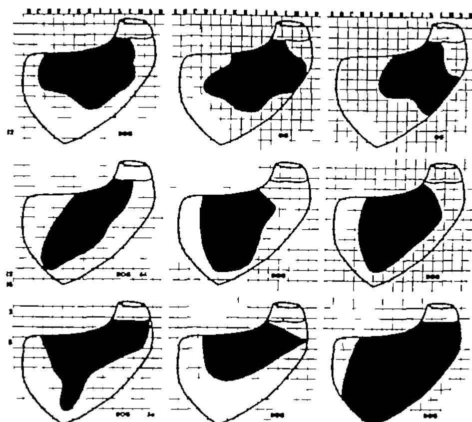


Fig. 4. Representative maps of right ventricular activation in the 7 dogs in which the free running false tendons were sectioned and of the 1 animal in which the main right bundle was severed. Black areas represent areas of maximum delay. Nos. *1535a* and *1535b* were recorded from the same dog at an interval of 3 weeks. The map marked *RBBB 1* was made from one dog in which the septal right bundle was completely sectioned.

those obtained by Lewis,[3] Harris,[4] and Cenender and associates.

After the sequence of normal activation had been determined, the free running false tendon strands were sectioned through the atriotomy. The canine right bundle branch normally extends from the common bundle in the region of the medial cusp of the tricuspid valve behind the papillary muscle of the conus downward to the anterior papillary muscle. At this level the RBB gives off several branches, some of which enter the septum and papillary muscle, whereas others (free running false tendons) traverse the right ventricular cavity from the base of the papillary muscle to the endocardial surface of the free wall. The open right ventricle of Dog No. 1536 photographed 4 weeks after sectioning of the free running false tendons is shown in Fig. 2*C*. The right ventricular free wall has been reflected to the left, and the cut edges of the main free running false tendon strand are denoted by arrows. The anterior papillary muscle is indicated by the right arrow. A minor strand was not sectioned in this dog. In Dogs No. 1582 and No. 1645 it was found at autopsy that several minor strands of conducting tissue had been left intact. In none of the hearts was there evidence of damage to the right ventricular free wall or to the right septal surface at the level of the right bundle branch.

Fig. 3 is a representative record used to determine the delay in activation time of the different right ventricular epicardial areas after sectioning of the free running terminal branches of the right bundle. The same left ventricular epicardial reference electrode was used to time right ventricular activation in both instances. In record *A*

which was obtained before cutting the false tendons it can be noted that the activation time of the left ventricular reference electrode (second tracing from the top) and that of the exploring electrode placed at the area H 5 on the right ventricular surface are nearly simultaneous The delay in activation time of this same right ventricular epicardial area (H 5) after sectioning is depicted in record *B* activation now is delayed by about 20 msec There also is a slight prolongation of QRS (less than 10 msec)

A typical example of the effect of sectioning the free running branches of the right bundle upon right ventricular epicardial activation time in the dog (No 743) is shown in Fig 2 *B* There was no change in the P R interval of the electrocardiogram in any of the dogs studied The numbers in the different epicardial areas of the right ventricle represent the delay in activation time after sectioning of the free running Purkinje fibers of the false tendon The area which exhibited the greatest delay is stippled As might be anticipated the magnitude of the delay that resulted from sectioning of the free running false tendons varied from individual to individual The magnitude of delay of activation of discrete areas ranged from 0 0 to 39 0 msec within a single heart the maximum delay in a given heart ranged from 16 0 to 39 0 msec However the general area of the right ventricular epicardium showing delayed activation was consistent (Fig 4) This region was located in the upper middle half of the right ventricular epicardium and included some of the right ventricular outflow tract In 2 dogs in which minor strands remained intact delays were somewhat less and the area of delay was less extensive The right ventricular activation map at the lower left and that in the lower middle of Fig 4 were made from the same dog at the time of operation and prior to autopsy (3 weeks later) respectively The amount of delay and the area of delay remained relatively constant The map in the lower right hand corner in the same figure shows the area of delay produced when the septal right bundle was sectioned at the level of the papillary muscle of the conus

D Electrocardiographic and vectorcardiographic studies Standard precordial and limb lead electrocardiograms[3, 7] were recorded on all dogs prior to operation and again at intervals of 1 2 and 3 weeks after the false tendons had been cut Fig 5

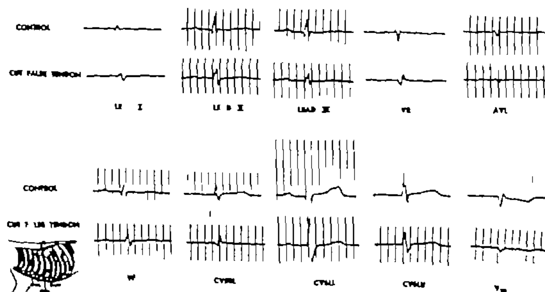


Fig 5 Representative electrocardiogram recorded before (control) and after sectioning of the free running false tendons Standard limb leads and precordial leads suggested by Lamont Insert in lower left corner shows position of precordial lead

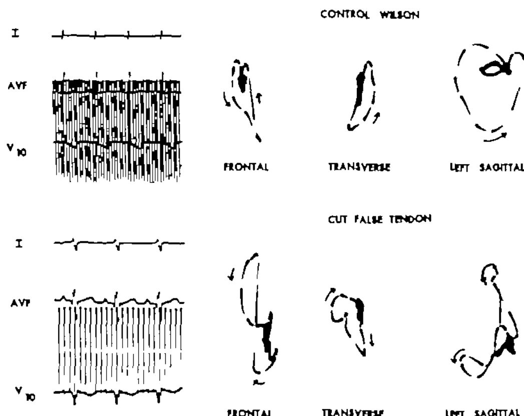


Fig. 6. Scalar leads used for recording the vectorcardiograms are shown at the left. Vectorcardiograms using the Wilson system were recorded before (control) and after sectioning of the right ventricular free running false tendons. These recordings are from the same dog as in Figs. 2, 5, and 7.

shows typical electrocardiograms from the same dog as in Fig. 2 (No. 743). A very slight increase in QRS duration (less than 10 msec.) was observed in this dog. In 4 of the 7 dogs no alterations in QRS duration were observed. This is consistent with results obtained by others.[4,13] In all 7 animals QRS durations fell within the range considered to be normal for the dog.[13]

If one compares the electrocardiograms recorded before (control) and after sectioning of the false tendons (Fig. 5), the most obvious changes are observed in Leads I, aV_R, and CV_6RL. CV_6RL corresponds approximately in position to the precordial Lead V_1 in man (see accompanying diagram—Fig. 5). In Lead I the ventricular complex differs from that of the control tracing in that it changes from a QR to an RS configuration; in Lead aV_R the R wave increases in amplitude and duration; and in CV_6RL the configuration changes from an RS to RSR' complex. Changes in the T wave were observed in 4 of the 7 dogs. A similar electrocardiographic pattern observed in man has been referred to as *partial right bundle branch block*.

The leads from which the equilateral tetrahedron vectorcardiograms in Fig. 6 were electronically derived are shown at the far left of the figure. These vectorcardiograms are from the same dog (No. 743) as the electrocardiograms in Fig. 5. Control recordings are shown in the upper tracings and vectorcardiograms from the same dog taken 2 weeks after operation are presented below. The orientation of the initial 0.004 to 0.008 second of the QRS is essentially unchanged, but thereafter the vectorcardiogram is markedly altered. In the frontal plane the direction of inscription of the QRS loop is changed from a counterclockwise direction in the control tracing to a clockwise figure of

eight inscription The major change is the marked shift of the terminal forces to the right and cephalically. In the transverse plane the direction of inscription also is changed from counterclockwise in the control to clockwise after sectioning of the false tendons and terminal forces are oriented to the right The postoperative record in the left sagittal plane likewise exhibits delayed terminal forces directed cephalically Only minor changes were observed in the orientation of the T loop These vectorcardiograms resemble those observed in the partial RBBB pattern of man

Detweiler[22] has observed as have others [3] that variations in the placement of the forelimbs may profoundly influence the form of the QRS complex in the canine limb lead electrocardiogram and thus in vectorcardiograms derived from limb leads The equilateral tetrahedron of Wilson is particularly subject to such changes In order to minimize variations in the scalar and vectorcardiographic recordings made in this study we consistently placed the dogs in right lateral recumbency with the limbs parallel to each other and perpendicular to the long axis of the body

MCFEE LEAD SYSTEM A corrected lead system designed for the dog by McFee [4] was also used to record vectorcardiograms (Fig 7) The general form of the QRS and T loops recorded by this system resembled those of the Wilson system There was little alteration in the direction of the initial portion of the QRS loop (first 008 sec) but as with the Wilson system the terminal portion of the QRS loop was directed cephalically and toward the right The direction of inscription of the QRS loop in the frontal and left sagittal planes was unaltered but in the transverse plane it changed from counterclockwise in the control tracing to clockwise after sectioning of the free running false tendons

E Chronic experiments on sectioning of the main right bundle In order to compare the partial right bundle branch block observed after cutting of the free running false tendons with complete bundle branch block complete sectioning of the main right bundle at the level of the papillary muscle of the conus was performed Fig

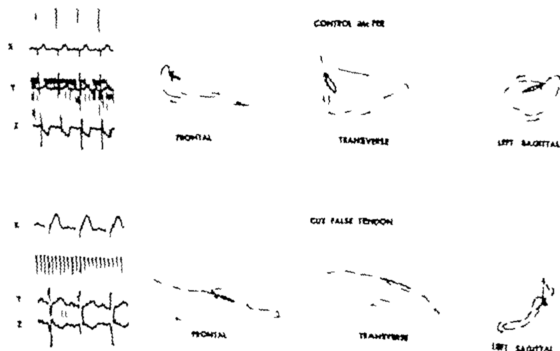


Fig 7 Scalar leads for recording vectorcardiograms using the McFee system are at the left with vectorcardiograms before and after sectioning shown at the right

8 A is a map of the normal activation of the right ventricle recorded prior to operation. As shown before in Fig. 2 A, the anterior third of the right ventricular epicardium was activated first, followed by the middle regions, the posterior aspects, and finally the pulmonary conus region. Area K9 was the site of earliest activation.

In B of Fig. 8, the magnitude and site of epicardial delay are indicated. The shaded area denotes the area of greatest delay. By comparing values in Fig. 8 with those in Fig. 2 B, one can observe that the delay in the respective areas which resulted from complete RBBB is much greater than that observed after sectioning of the free running false tendons. Similarly, the area of delay also is greatly increased by sectioning of the main right bundle.

F. Electrocardiographic and vectorcardiographic changes. Fig. 9 shows electrocardiograms which were recorded before and after the right bundle branch had been cut. It can be seen that in all leads the QRS duration is slightly more than double the normal value.

Sectioning of the RBB had effects on the electrocardiogram (Fig. 9) and vectorcardiogram (Figs. 10 and 11) similar to those produced by cutting the free running false tendons, but more marked in degree. The total QRS duration doubled (0.04 sec. preoperatively, 0.08 sec. after sectioning of the RBB). In the ECG, large, wide, notched S waves developed in Leads I, II, and III, in Lead aVF, and in the left thoracic leads, and a wide notched R in Lead aVR. In lead CV₁RL (equivalent to Lead V₁ in man) the complex changed from an RS in the control tracing to a wide notched R, having a small initial component followed by a wider component of higher amplitude.

Vectorcardiographic changes in QRS and T loop configuration were similar in the Wilson and McFee systems. The initial 0.008 sec. of the QRS loop was practically unchanged in direction, being oriented cephalically, ventrally, and toward the right before and after sectioning of the right bundle branch. The magnitude of the initial portion, however, was reduced by approximately one half, and although the loop continued in a similar direction for an additional 0.008 to 0.016 sec. in the control tracing, it shifted immediately toward the left in VCGs recorded after the RBB had been cut. The direction of inscription of the QRS loop changed from counterclockwise to clockwise in the frontal and transverse planes and the configuration of the loops became irregular; efferent and afferent limbs crossed over at several points. The mid portion of the QRS loop (0.020 to 0.028 sec.) remained essentially unchanged, being directed caudally, ventrally, and toward the left. The most marked change occurred in the terminal portion of the loop, which, after sectioning of the RBB, was prolonged and changed in direction. Rather than being oriented dorsally and toward the left as in the control tracing, the delayed terminal portion was directed ventrally, cephalically, and to the right.

The T loop also changed in its orientation after sectioning of the RBB. In the control tracing it was directed ventrally, cephalically, and to the right; after operation it shifted almost 180 degrees, being directed caudally and to the left (in a direction opposite to the late portion of the QRS loop).

Discussions

In the foregoing studies, the sequence of activation of the right ventricular epicardium was determined by measuring the onset of activation at 20 to 30 representative epicardial sites, both during normal atrioventricular activation and after sectioning of either the free running false tendons or the main right bundle branch (RBB). An atriotomy was made to permit sectioning of the right conduction system. Since no change occurred in the P-R interval and a ventriculotomy was not made, delays in ventricular activation which occurred can be assumed to have resulted from interruption of the specialized right ventricular conduction pathways.

The results obtained from normal hearts agree with those of Lewis,[18] Harris,[20] and Genender and associates.[21] The point of earliest depolarization was observed in the lower and anterior apical parts of the right ventricle. Activity next occurred in the mid regions of the epicardium, the posterior basilar parts, and pulmonary

conus regions were activated last. These findings probably can be correlated with the fact that the anterior and middle parts of the ventricle receive the free running false tendons which contain the terminal branches of the right bundle whereas Purkinje tissue generally is lacking in the pulmonary conus and posterior septal regions.[8, 13, 14]

In Fig 12 *A* and *B* *Controls* the activation times of the different right ventricular (RV) epicardial regions are indicated by dots on QRS of Lead II recorded from Dogs No 743 and No 111 during normal

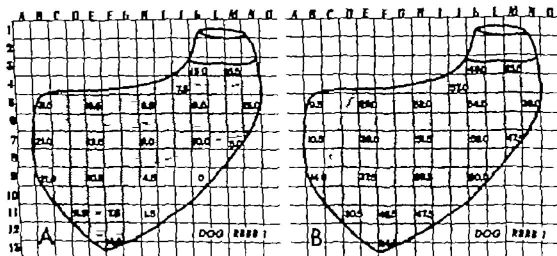


Fig 1 4 Map showing the normal sequence of epicardial activation. The numbers in each area show the activation time in milliseconds after the earliest point on the epicardial surface of the right ventricle (K9). The shading is employed as in Fig 2 1 to indicate early, intermediate and late activation. One point N5 should have been included in the area of light shading. *B* Map showing the delay in activation of the same epicardial areas produced by section of the right bundle branch. The numbers show the difference in activation time of each point in milliseconds between *A* and *B*. As in Fig 2 *A* the area of maximum delay is shaded.

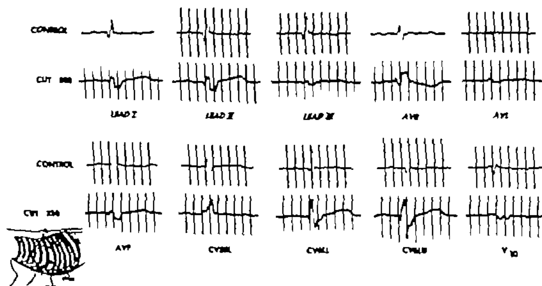


Fig 9 Electrocardiograms recorded before and after sectioning of the RBB at the level of the papillary muscle of the conus. Time lines at intervals of 10 msec. Position of precordial leads is shown in insert.

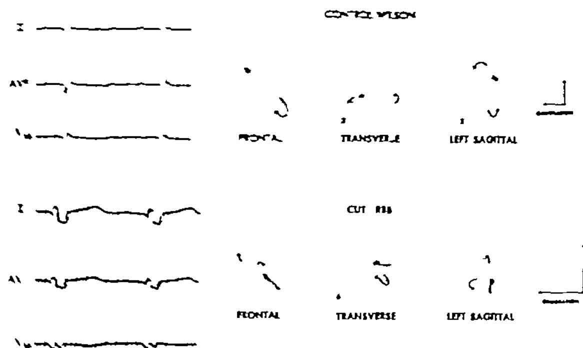


Fig. [illegible] vectorcardiograms (Wilson system) recorded before and after sectioning of the RBB [illegible] for record obtained after sectioning.

intraventricular activation; the respective areas on the RV map are indicated below the QRS complex.

All the RV epicardial sites are activated during the R wave and within an interval of about 25 msec. The fact that these measurements and the QRS complex were recorded during operation with an open chest may have altered the activation sequence and the QRS configuration to a slight degree. The over-all contribution of the right ventricle to the QRS complex cannot be ascertained from our studies since the time of activation of

canine experiments we have demonstrated that delay of activation of the right ventricle occurs when the free running false tendons (terminal parts of the RBB) are subjected to stretch or other damage. We believe that many cases of incomplete right bundle branch block which are attributed to damage of the main RBB are in fact due to damage of the peripheral parts of the RBB which run in the false tendons of dogs or in the moderator band of man.

The effect of sectioning of the false tendons on RV epicardial activation time can

served in the respective RV epicardial areas Thus the respective RV epicardial areas were activated within normal QRS duration [3] even though an alteration in the configuration of the QRS complex could be observed The posterior basilar regions were activated last as might be anticipated from the distribution of Purkinje fibers and the observation of Amer and associates[24] that sectioning of the right ventricular false tendons delayed activation of the posterior part of the RV septum by 10 to 15 msec The fact that about 45 msec were required for RV epicardial activation after sectioning although activation was complete within 25 msec during control measurements would seem to indicate that the sequence of activation was altered Our findings do not support the conclusions of Sodi Pallares[22] who found that the free wall of the blocked side of the heart was activated in a normal sequence

Complete RBBB was produced in order to compare the effects on right ventricular epicardial activation time of sectioning of the main RBB with those obtained after sectioning of the free running false tendons The results are shown in Fig 12 *B* wherein the activation of 21 RV epicardial areas is indicated on the QRS complex of Lead II before (control) and after the main RBB was cut at the level of the papillary muscle of the conus (Fig 12 *B* *bottom*) Our results essentially confirm those of others in that (a) the left ventricle appears to be nearly completely activated before RV epicardial activation [4] (b) the activation sequence of RV epicardial areas does not occur as during normal activation [9] (c) there were delays ranging from 9 5 to 58 msec in RV epicardial activation of different areas and (d) ECG and VCG changes characteristic of complete RBBB were obtained

The observation that activation of the RV free wall is so markedly delayed does not seem to concur with the conclusion of Anselmi and associates[24] that only delayed septal activation is responsible for the ECG changes of RBBB The only epicardial region in which activation was not markedly delayed after sectioning of the main RBB was the posterior septal area This may result from the fact that the posterior part of the RV septum is

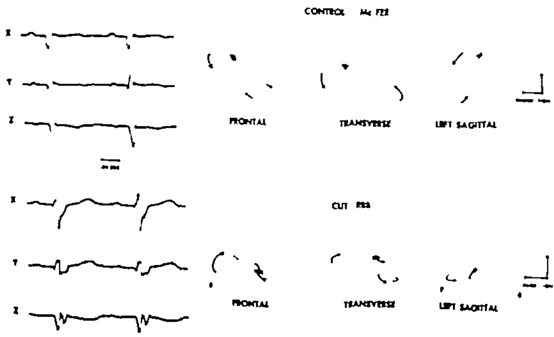


Fig 11 Scalar leads and vectorcardiograms recorded before and after sectioning of the RBB using the McFee lead system

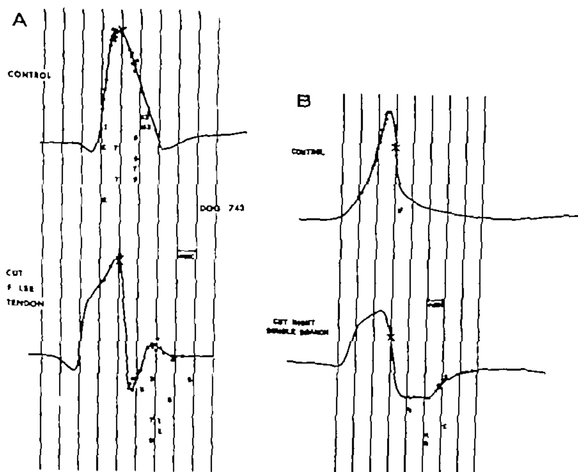


Fig. 12. A. Comparison of the QRS complexes (Lead II) recorded before and after sectioning of the false tendon of the right ventricle; these records were obtained from the same animal used for Figs. 2, 5, 6 and 7. The time of activation of specific areas on the epicardial surface is indicated by the dots placed along the trace; the designation of the epicardial areas activated during each 10 msec. interval is listed below the trace. The time of activation of the site of the left ventricular reference electrode is indicated by the X on both traces. B. The same conventions described for A are employed to indicate the changes in the QRS complex of Lead II produced by sectioning of the septal right bundle branch.

activated from the left ventricle in some dogs.[39] In comparison, incomplete RBBB caused by sectioning of the terminal branches of the right bundle (free running false tendons) caused smaller delays in RV epicardial activation; 39 msec. was the longest delay observed.

Summary

The onset of activation of 20 to 30 right ventricular epicardial areas has been determined before and after sectioning of the right ventricular free running false tendons or the septal right bundle; the corresponding electrocardiogram and vectorcardiogram are shown. It is postulated that many cases of incomplete right bundle branch block result from damage to the free running false tendons in dogs (moderator band in man). Delay in activation of the free right ventricular wall appears to be important in producing electrocardiographic changes in both conditions. Microelectrode experiments on isolated tissues demonstrated that the basilar part of the main right bundle branch located above the anterior papillary muscle does not excite the adjoining right septal musculature.

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The limits of information in the vectorcardiogram. Comparative resynthesis of body surface potentials with different lead systems

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Various criteria have been suggested for judging electrocardiographic and vectorcardiographic lead systems: the ability of lead systems to reproduce the magnitude and orientation of a dipole in a torso model,[illegible] their ability to suggest to an interpreter certain anatomic or physiologic abnormalities,[illegible] the presence or absence of familiar clinically significant electrocardiographic configurations of wave form,[illegible] and the degree to which geometric transformation allows information obtained by one system to be presented in the form of another.[illegible] These methods have all lacked recourse to the biologic source for either additional electrophysiologic data or an estimate of the total amount of ascertainable information.

Because application of principal factor analysis has made it possible to estimate quantitatively the maximum information available in extensive surface electrocardiographic recordings,[illegible] we have utilized this method to assay the relative information content of five vectorcardiographic lead systems. Thus the present study will present a comparison of these lead systems in terms of the degree to which each is able to transmit all the available electrocardiographic information concerning wave form on the body surface.

Methods and materials

In a previous study, electrocardiographic recordings of high speed and fidelity were obtained by the systematic spacing of unipolar leads over the thorax of both dog and man.[illegible] Potential values were then obtained from temporally matched QRS complexes at 10 msec. intervals in the human subject. These values were interpolated down to 2 msec. intervals with the aid of a digital computer to produce digitized QRS wave forms corresponding to

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the original recordings.[23] Factor analysis of the total set of 180 QRS wave forms yielded 8 uncorrelated or unique wave forms (Fig. 1), which are here assumed to represent the upper limit of available surface information concerning ventricular depolarization.[23]

In the present study, vectorcardiograms were obtained from the extensive data on surface potential by digital computation. According to the originators' instructions, the appropriate recording sites from the 180 lead electrocardiogram were either selected or established by interpolation for the five vectorcardiographic systems tested.[11,23] Next, the appropriate weighting factors from recommended resistances or gain factors were mathematically applied. The IBM 1620 Electronic Data Processing System was instructed to receive the instant by instant wave form data, to apply the weighting factors, and to punch out the results, first in the form of scalar VCG leads (Fig. 2) and then in the form of vector loops (Fig. 3). Likewise, the first three principal factors—which are themselves truly orthogonal to each other—were cast into vectorial form.

Because certain advantages were observed among the VCG systems with relatively greater anatomic spread of opposed sets of electrodes, a special VCG system* was improvised along the lines originally recommended by McFee and Johnston.[18] For X, left and right components each consisted of 5 equally weighted electrodes (4 at the corners of a 6-cm. square and 1 in the center). These were placed on each side of the chest and centered on the junctions of the anterior axillary lines and the level of the fifth intercostal space. For Z, similar squares of 5 electrodes each were centered over the left parasternal line at the fifth intercostal space and over the directly posterior point on the back. For Y, the upper component consisted of 20 equally spaced points about the circumference of the chest at the level of the suprasternal notch, and the lower component was a similar belt of 20 points at the level of the umbilicus. The vectorcardiographic leads and loops of this special system were derived by electronic computation in the same manner as in the other systems.

The vectorcardiographic systems were next normalized for further comparisons (Figs. 2 and 3). This was done initially upon automatic calculation of the polar vector[9] and maximum QRS vector[11] by rotational transformation of axes corresponding to the method of normalization† of McFee and associates.[22] We soon found it more expeditious for digital calculation to normalize by applying factor analysis to the X, Y, and Z wave forms as recommended by Young and Huggins.[9] A computer program was designed to take a set of VCG leads and resynthesize either a given QRS complex or the principal factors, thereby allowing a point-by-point numerical evaluation and comparison of effectiveness. The leads of the vector systems were further analyzed as to the topographic distribution of the X, Y, and Z components found in the QRS wave forms on the surface

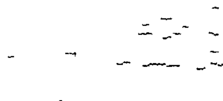


Fig. 1. Principal factor wave forms of the QRS complex derived by factor analysis of 180 thoracic QRS wave forms.[23] Note that factors 1 and 2 exhibit the maximum amplitudes and that factor 1 (resembling closely X in configuration) is principally positive, and that factor 2 is equiphasic (resembling such a lead as Y).

*W[illegible] used th[illegible] special [illegible] to indicate that the [illegible] effect of [illegible] for [illegible]

†Th[illegible] used in the [illegible] by McFee and associates[22] to indicate [illegible] loop [illegible] standard [illegible] and therefore [illegible] that plane and [illegible] of the [illegible] plane and [illegible] the axis

of the chest. Calculations were made for each recorded QRS or derived principal factor of the "information" in the original wave form (root sum square of its deviation from base line) and the "error" of reproduction of information (root sum square of the deviation of the VCG derived wave form from the original). Effectiveness was estimated by determining the per cent of error relative to information.

Results

The first two normalized leads of each vectorcardiographic system strongly resembled the first two principal factors (Figs. 1 and 2). As may have been expected, the broadside projections of the vector loops resembled the result when these two factors were cast into vector loop form (Fig. 4). Table I summarizes the error encountered in attempting to resynthesize the eight principal factors from each of the vectorcardiographic systems. Note that for the corrected systems* factors 1 and 2 were well reconstructed. The first two factors were not so well resynthesized by the uncorrected systems, but the third factor was relatively better handled by the uncorrected systems—especially the cube. However, with the multielectrode lead field ("special") system there was both good reproduction of principal factors 1 and 2 and improved resynthesis of factor 3. Little or no resynthesis of factors 4 through 8 was obtained with any of the systems (Fig. 5).

Discussion

Limitation of the method. The theoretical basis for this study rests on two major sets of assumptions. First, the electrocardiographic information (as represented by the QRS complex) at all sites (of which 180 is assumed to be an adequate sample) upon the chest is reducible to a small number of component wave forms which we call "principal factors." Thus, if we know what the principal factors are for a given subject, we know the limit of electrocardiographic information available from that subject. Second, since it is possible to determine the relationship between the leads of any vectorcardiographic system and the principal factors, reference to this relationship may be used as an estimate of how much of the total information can be carried by a given lead system and, consequently, how far short that system may fall in its report.

Determination of the principal factors is subject to error in the event of temporal mismatching of any of the records.[1,12] We have attempted to minimize as much as possible artifacts arising from lack of simultaneity in recording (1) by utilizing only those complexes recorded during the resting phase of the respiratory cycle, (2) by doing the entire surface mapping at one sitting as rapidly as possible, (3) by immobilizing the subject as much as possible to avoid positional variations from

Fig. 2. *a*, Scalar leads X, Y, and Z of the axial vectorcardiographic system obtained from the surface potentials of the same subject from whom the principal factors shown in Fig. 1 were derived. Similar plots were computed of the simultaneous configuration of the leads of the other vectorcardiographic systems. (See text for details.) *b*, Scalar leads of the axial vectorcardiographic system *after normalization* (rotational transformation of axes)—in this instance by means of factor analysis. Note the striking similarity in configuration between the first two of these leads and factors 1 and 2 of Fig. 1.

*The SVEC-III, axial, and Frank systems [illegible] referred to as "corrected" lead systems [illegible] the cube [illegible] referred to as "uncorrected." The term "corrected" lead system [illegible] that [illegible] by the [illegible] of [illegible] by [illegible] of [illegible] lead field theory—has been used [illegible] the basis of experiments [illegible] to obtain the lead [illegible] orthogonal [illegible] of the heart. The "uncorrected" lead systems that [illegible] have the design of the lead systems.



Fig. 3 Plane projection of the axial spatial vector loop before (a) and after (b) normalization. These vector loops correspond to the scalar lead shown in Fig. 2. The time interval between successive dots 2 msec.

cycle to cycle (4) by recording a constant control lead for time alignment and (5) by comparing the digital plots of the wave forms with the original data [1, 11]. A disadvantage of using the principal factors as a criterion of information lies in the great amount of time required for their computation for each subject after all the information was put into digital form approximately 48 hours of computer processing was required to reduce 180 QRS wave forms to the eight principal factors [11].

It should be observed that for resynthesis of a QRS wave form from principal factors or for resynthesis of principal factors from VCG wave forms it is more meaningful to use the concept of error as a per cent of the total original information than resynthesis as a per cent of that same total. This difference results from the fact that the error may be in the form of either overshoot or undershoot and thus the root sum square of error is very much like the common concept of standard deviation. It follows that neither the relative magnitudes of the resynthesized wave compared to the original nor the remainder after subtracting the error from a total of 100 per cent is satisfactory as an estimate of adequacy of resynthesis. We have therefore confined ourselves to speaking of error alone.

Relative information content of the vectorcardiographic leads and the eight principal factors. The corrected systems reproduced relatively well the information in the first two of the eight principal factors. On the other hand although the uncorrected systems fell short on the first two factors their better showing on factor 3 raised their total information content. Thus all the VCG systems approached a total error of about 20 per cent.

As pointed out by Scher [4] if only three independent wave forms were necessary to account for all surface data a dipole is one of the possible equivalent explanations of the cardiac generator. As demonstrated by Young and Huggins [4] a vectorcardio

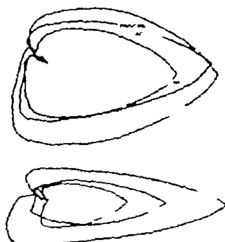


Fig. 4 Comparison of the broad side or en face views of the normalized vector loops and a loop made from principal factors 1 and 2. The scale for the cube and tetrahedron has been doubled to make them comparable in use with the others. The broad side view of the loop of the special lead field vectorcardiogram is not illustrated but was almost superimposable upon that of the axial vectorcardiogram shown here.

gram can be made with three factors whether or not anatomic orthogonality is preserved or anatomic orientation is discernible. But if seven or eight such waves are necessary, undoubtedly a cardiac generator of higher order must be expected. The bridge between a mathematically satisfactory equivalent cardiac generator which accounts for all the surface information and the physiologic characteristics of the real cardiac generator remains to be found.

We wish to suggest, as seen in Fig. 6, that factor 1 and factor 2 may describe the first order component of the equivalent cardiac generator, i.e., the plane vector loop or dipolar component. In this event the remaining factors may contain the nonplanar component of the dipole *and* higher multipolar components. With factor 1 and factor 2 *only* a 20.6 per cent error remains in reconstruction of all of the information on the chest surface; with factors 1, 2, *and* 3 the error is reduced to 14.6 per cent (Table I).[18] With all three leads of any of the vectorcardiographic systems (see Table II) the average error in reproduction of surface information also varied between 20 and 15 per cent—ranging from 20.0 per cent for the Frank system to 15.9 per cent for the "special" lead field system. Note in Fig. 4 the solid black line describing a vector loop constructed strictly from factor 1 and factor 2. The normalized vectorcardiographic loops from five conventional systems largely have the same contours, although the relative size of the major and minor axes vary somewhat. Reference to Table I, however, indicates that relatively greater departure in contour occurred in the uncorrected systems. Higher order multipolar, that is nonvectorial, components may have entered into the formation of these uncorrected systems and were read on the vectorcardiogram as evidence of departure from the plane of the vector loop. This is also suggested in Fig. 5, in which the cube system seemed to be relatively effective in resynthesizing factor 3. This may be because the distant, off-plane placement of the leads in the cube system rendered it especially sensitive to multipolar components or to the nonplanar component of the vector loop.

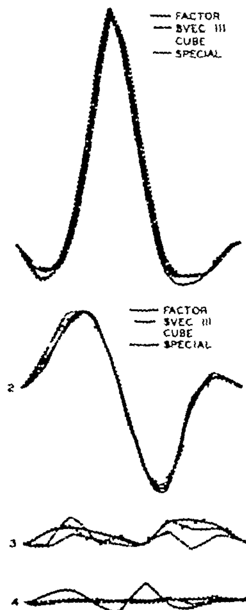


Fig. 5. Resyntheses of principal factor 1, 2, 3, and 4 from the leads of three representative vectorcardiographic systems. The original factor in each instance is described by the solid black line and the resynthesized wave form is shown by the dashed line for the SVEC III, the dotted line for the cube, and the broken line for the special vectorcardiographic lead. Note that all systems reproduce factor 1 and 2 well—the relatively greater error from the cube is visible but slight. Factor 3 is reproduced erratically and factor 4 (typical of factor 4 through 8) hardly at all.

Awareness of the regions of sensitivity to the dipolar component of the cardiac generator made it easy to construct a simple lead system which improved upon

Table I

Factor	Error in reproduction of thoracic QRS by principal factors*	Individual errors in reproduction of principal factors by VCG systems†					
		SVEC III	*Axial*	*Frank*	*Cube*	*Tetrahedron*	*Special*
1	46 8	4 4	7 8	4 3	3 8	4 4	1 6
2	70 6	10 6	5 3	10 4	12 0	27 4	4 0
3	14 6	93 2	89 8	84 9	46 7	6 9	45 1
4	11 9	9 9	87 3	97 6	9 8	85 7	99 3
5	9 1	88 3	97 7	8 3	91 3	94 2	99 4
6	6 9	84 0	88 5	86 3	99 7	99 0	97 5
7	3 6	92 4	85 1	93 0	98 8	98 8	93 1
8	0 3	91 1	98 2	94 3	99 8	95 3	100 0

*Per cent average error in reproduction of the 180 original QRS wave forms. As each principal factor is successively applied the error diminishes as shown.

†Not cumulatively applied. For example, factor 1 was reproduced from leads X, Y, and Z of SVEC III with 4 4 per cent error but factor 3 was reproduced from the same leads with 93 2 per cent error.

Table II Average error in resynthesis of 180 QRS wave forms from three parameters

	Per cent
Principal factors 1, 2 and 3	14 6
X, Y and Z Leads	
SVEC-III	19 7
Axial	18 4
Frank	20 0
Cube	16 4
Tetrahedron	19 7
Special	15 9

the previous ones in terms of reproducing the vector loop components (factors 1 and 2) as well as to obtain more critical information of the nonplanar component of the dipole as noted by the improvement in reconstruction of factor 3. In fact we may view in a new light the advantage of the lead field technique of voting together opposed sets of many electrodes. The original proposal was based on the notion of "bracketing the heart" with a sufficient number of electrodes for a given lead to produce a uniform lead field (i.e., many roughly parallel projective lines or lead axes) through the heart region.[14] Thus this technique theoretically produced lead fields which were sensitive to dipolar signal and relatively insensitive to higher-order signal. Examination of the surface distribution of principal factors now suggests to us not only that the grouping of opposed sets of leads results in an averaging phenomenon but also that the averaging specifically produces cancellation of nondipolar or multipolar contributions. Because the strongest *common* signal pre

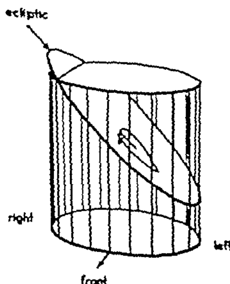


Fig. 4. Diagrammatic representation of the torso illustrating the orientation of the plane of the dipolar component of the electrocardiographic generator. Note that the plane of the vector loop is the surface of the best-fitting line designated the ecliptic. Near the ecliptic, factor 1 and 2 play a relatively large role in contribution to and resynthesis of the surface QRS wave form. Farther from the ecliptic the remaining factors show increasingly significant contribution to the local QRS wave form.[21] See text for discussion.

sented to several linked electrodes is the dipolar signal (factors 1 and 2—and some of factor 3), it emerges as the dominant signal. However, the expressions of the higher order signals (remainder of factor 3 and factors 4 through 8) vary widely within given surface regions as small as 6 cm. square and therefore have small net effect when averaged.

Anatomic relationship between normalized vectorcardiographic leads and the principal factors. The strength or relative amount either of each of the principal factors or of each of the vectorcardiographic leads at each electrode site may be determined by solution of simultaneous equations.[13] The *anatomic orientation of the first normalized* lead of a vectorcardiographic system is effectively the electrical axis of the heart. When combined with this first lead, the axis of the second normalized lead characterizes the plane of the loop. The axis of the third normalized lead then is equivalent to the polar vector. Any information on this axis describes departures or aberrations from the electrical plane of the heart (plane of the spatial vector loop).

How do the anatomic distributions of normalized vectorcardiographic leads relate to the anatomic distribution of intensity of the principal factors derived from comprehensive mapping of the chest? The first two factors have anatomic distributions of intensity very similar to that of the first two normalized leads of any of the three lead systems. In this way it is satisfactory for us to consider that these first two axes and, appropriately, the first two factors describe a spatial vector loop with its successive instants all coplanar—similar to the essential plane of the loop[3] of the vectorcardiogram as shown diagrammatically in Fig. 6. But in contrast to the vectorcardiographic case, the third factor does not have a simple anatomic distribution and does not necessarily merely reflect departures from planarity.[14] All of the principal factor wave forms beyond the second quite possibly contain information of higher-order (multipolar) nature in addition to any indication of nonplanarity of the first order (dipolar) component.

A word of caution is appropriate here. The location on the chest of the distributive maxima for principal factors 1 and 2 are near coincident with those of the first two leads of any of the normalized VCG systems. It might be tempting to conclude that, with the application of four electrodes centered on these maxima, two leads would result which contain all the appropriate first order (dipolar or vectorial) information and as such would be a satisfactory screening electrocardiogram. However, we may reasonably expect considerable variation of such ideal electrode sites within the normal population and even more likely variation when abnormal individuals are considered. Review of the history of electrocardiography suggests that considerable accumulation of observational data and careful theoretical treatment should precede any clinical adventures into another electrocardiographic lead system.

Summary

This has been a report on a method of evaluating the information content of the vectorcardiogram. Systematically spaced recordings of the QRS complex about the human chest—when subjected to factor analysis—reduced to eight component wave forms or principal factors. These set the limits of information. The ability of any VCG lead set to reproduce these principal factors measures its quantitative content of information and may give some indication as to the qualitative content. VCG lead systems are designed to present the vector or dipolar component of the heart signal; this report may be quadripolar if the lead system is sensitive to nondipolar components of the signal.

The corrected systems reported the planar vector loop (factors 1 and 2) rather well; the uncorrected systems were poorer at reproducing factors 1 and 2 but somewhat more sensitive to factor 3—which contained either nonplanar dipolar or nondipolar components. Usable information was restricted by an error of approximately 20 per cent in all current systems. Awareness of these limitations made it possible to suggest a means by which the information content could be improved.

We are indebted to Dr. Charles W. Shepherd for his aid in placing the facilities (USPHS FR 00001) of the University of Tennessee Computer Center at our disposal, to Martha Hutcheson, Judy Latham

and Ann M Eachern for a i tance in data processing and to Wallace Marquardt and Irvin Jaynes for as istance in preparation of the illustrations

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Cardiac function during perfusion of the circumflex coronary artery, with venous blood, low-molecular dextran, or Tyrode solution

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In previous investigations we have reported that perfusions of venous blood or colloidal isotonic solutions at systemic pressures for 30 minutes into the anterior descending coronary artery of normal and even previously hypertrophied hearts did not alter the rate of heartbeat nor the aortic and left atrial pressures.[1] After these results the following interesting question arises: What could be the result on the cardiac function if a coronary artery with a greater flow, such as for example the circumflex coronary artery, which supplies about 70 per cent of the left ventricular myocardium, were to be perfused with the above-mentioned fluids under various pressure conditions. Such perfusions have been reported in the literature[4] in the isolated heart, *but not in the beating heart which maintains the work load of the circulation.* The following experiments have been performed in order to study cardiac function during several perfusions of the circumflex coronary artery.

The first subject to be investigated was the *functional changes in the heart during perfusion of the circumflex branch of the left coronary artery with venous blood at a higher flow rate of 25 ml. per minute for a period of 60 minutes, after which low-molecular dextran was perfused for 30 minutes at the same rate.*

Methods

Fifteen unselected young dogs which weighed between 14 and 16.5 kilograms were used. Anesthesia was induced and maintained with intravenous Nembutal, 25 mg. per kilogram. Cyclic positive pressure insufflation of the lungs with 100 per cent oxygen was maintained, and the thorax was opened through the fourth left intercostal space. The inferior vena cava and descending aorta were cannulated through one femoral vein and artery; the cannulas were connected to an electromanometer. The standard ECG leads were recorded. It is important at this stage to note the variation in the coronary artery in these experimental animals. The angle between the circumflex and anterior descending coronary arteries was vascularized from a branch arising from the anterior descending artery in 10 dogs and from the circumflex artery in 5 dogs. The branches of the anterior descending artery were distributed predominantly to the left ventricle in 11 dogs (type A) and to both the

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left and right ventricles in 4 dogs (type B).[1] The circumflex coronary artery was then freed, prepared for about 3 cm and ligated as near as possible to its origin. The distal part of the artery was then cannulated with a 1.65 mm nylon cannula with a terminal hole. The catheter was inserted into the lumen of the artery about 1 cm distally from its origin. The tip of the catheter was secured some millimeters more distal to the first auricular branch of the artery, the orifice of which was thus occluded by the side wall of the catheter. Between the level of the ligature of the circumflex coronary artery and the tip of the catheter only some smaller ventricular branches were occluded by the side wall of the catheter. Medium sized branches were occluded only in 3 animals. The catheter was connected to a strain gauge and back pressures of the circumflex coronary artery were recorded. These pressures were between 16.2 and 50.40 mm Hg. Heparinized venous blood (5 mg of heparin per 1 000 ml. of blood) obtained from donor dogs (the oxygen content of which was about 14 volumes per cent and the temperature 37° C.) was then perfused at a systemic pressure level of about 150 mm Hg into the distal part of the circumflex coronary artery (Fig. 1). The perfusion rate was adjusted to 25 ml. per minute. The same amount of perfused blood was extracted each minute by phlebotomy. Aortic and inferior vena caval pressures and the ECG were continuously recorded. Every 10 minutes the perfusion was stopped and the catheter was connected to the electromanometer so that back pressures could be recorded. The perfusion was then continued. After 60 minutes of perfusion with venous blood a solution of 6 per cent low molecular dextran in normal saline (Rheomacrodex) of 40 000 molecular weight at 37° was perfused by the same technique at the same rate for 30 minutes. The starting flow rate was 25 ml. per minute in 10 dogs. In the other 3 it was 4 ml. per minute and then gradually increased to 25 ml. per minute within 2 minutes. In 8 dogs the

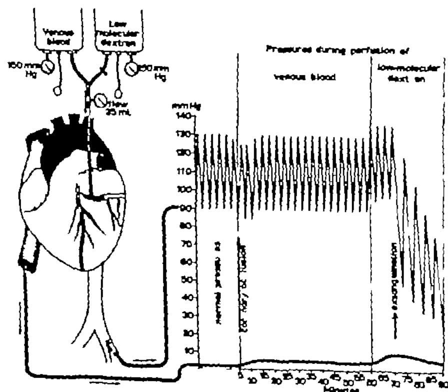


Fig. 1. Venous blood, low molecular dextran or Tyrode solution perfused with a flow rate of 25 ml. per minute into the circumflex coronary artery.

perfused dextran was bubbled for 1 hour before perfusion and during perfusion with oxygen through a porous aquarium stone at a rate of 2 liters of oxygen per minute. In the other 7 dogs the perfused dextran was not oxygenated. During the first 10 minutes of perfusion of dextran, venous blood was not extracted in 10 dogs. After perfusion of 250 ml. of dextran, phlebotomy was performed. In 5 dogs phlebotomy was performed from the starting moment of perfusion of dextran. Every 10 minutes the perfusion of venous blood or dextran was stopped for from 30 seconds to 5 minutes and the back pressures of the artery were recorded.

Results

All dogs survived these perfusions until the planned time of sacrifice. During cannulation, ventricular fibrillation occurred in 4 dogs. The heartbeat was restored by instituting heart massage and electrical defibrillation. Between a few seconds and 1 minute after the occlusion of the circumflex artery, the left lateral and posterior surfaces of the left ventricle became cyanotic. The limits of this change in color were well demarcated. The electrocardiogram showed marked alterations in the S-T segment, essentially in Leads II and III, with notching and other deviations in QRS complexes, as well as extrasystolic irregularities. The aortic pressure decreased by 10 to 15 mm. Hg and the venous pressure increased 1 to 6 mm. Hg in 11 dogs. In the other 4 dogs the aortic pressure remained unchanged. Only the venous pressure increased 2 to 4 mm. Hg. Between 1 and 2 minutes after the perfusion of venous blood was begun, the extrasystoles decreased or even disappeared and the normal heartbeat was restored. During the first 3 minutes of perfusion, ventricular fibrillation occurred in 2 dogs in which the venous perfusion was started more abruptly. The heartbeat was restored by instituting heart massage and defibrillation. In a group of 8 dogs the perfusion was started with a low flow of 4 ml. per minute and then increased to 25 ml. per minute within 2 minutes, but fibrillation did not occur. During perfusion the venous pressure decreased 2 to 4 mm. Hg but did not reach the preocclusive level. The aortic pressure increased to the preocclusive level in 11 dogs and to slightly under this level in the other 4 (Figs. 1 and 2). The average back pressure during perfusion was between 25/15 and 16/10 mm. Hg (Fig. 3). The back pressures could be stabilized and recorded 30 to 50 seconds after the perfusion was stopped. The ECG records have shown a decrease in the extrasystoles. The postocclusive alterations in the ECG persisted during perfusion of venous blood.

Immediately after the perfusion of oxygenated (in 8 dogs) or nonoxygenated (in 7 dogs) dextran was started, the extrasystoles increased and in 4 dogs ventricular fibrillation occurred. The perfusion was then stopped. The heartbeat could be restored by instituting heart massage and defibrillation. The perfusion was then continued uneventfully until the end of the experiment. In the group of 5 dogs in which dextran was perfused initially at a lower flow rate of 4 ml. per minute and was then increased to 25 ml. per minute within 2 minutes, fibrillation did not occur. When venous blood was not extracted during the first 10 minutes of perfusion of dextran, the aortic pressure was about equal to or even exceeded the preocclusive level. The venous pressure gradually increased 4 to 8 mm. Hg. No differences were observed between the perfusion of oxygenated and nonoxygenated dextran. In the group of dogs in which phlebotomy was immediately performed after the starting moment of perfusion, the aortic pressure decreased 10 to 30 mm. Hg during the first 5 minutes of perfusion and then decreased progressively until cessation of the perfusion. The already slightly increased venous pressure remained unchanged or decreased slightly. When the perfusion was stopped in order to measure back pressures, a period of 3 to 5 minutes elapsed until blood reappeared in the cannula and the back pressures were stabilized and measurable (Fig. 6). The average value of the latter was 25/10 mm. Hg. During the time the artery was not perfused, the pressures remained unchanged. Between 1 and 2 minutes after the starting moment of perfusion of dextran, the previously cyanotic region of the left ventricle became whitish. This color extended progres-

Molecular weight of 40,000.

sively into the limits of the distribution of the anterior descending coronary artery, pink areas of the anterior surface of the left ventricle. In each instance in which the perfusion was stopped for 3 to 5 minutes the whitish area remained unchanged or decreased 10 to 20 per cent of diameter. The same alterations as before were found in the ECG during perfusion of dextran. After the 30 minutes of perfusion of dextran the dogs were sacrificed. The temperature of the esophagus at the end of these perfusions and exsanguinations was decreased by 2 to 4.5° Celsius. Heart weights were obtained after transection of the great vessels at their bases and complete excision of the pericardium. The calculated predicted ratio of heart weight to body weight on the basis of the formula of Herrmann[8] showed no evidence of increased heart weight due to edema after perfusion of dextran.

Summary of results. Perfusion of venous blood at systemic pressures at a flow of 25 ml. per minute for 60 minutes to the circumflex coronary artery of 15 dogs did not alter the heartbeat. The aortic pressures increased to the preocclusive level

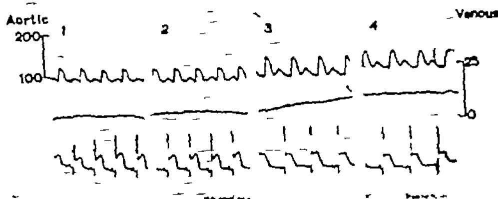


Fig. 2. Dog No. 8, first group. 1, At 10:00 A.M. Occlusion and cannulation of the circumflex coronary artery. Aortic pressure decreased. Venous pressure slightly increased. Anoxia of the myocardium. 2, At 10:35 A.M. Venous blood perfused for 30 minutes through the circumflex coronary artery at a rate of 25 ml. per minute. The same amount of perfused blood extracted by phlebotomy. 3, At 11:05 A.M. Low molecular dextran perfused at a rate of 25 ml. per minute. Exsanguination is not performed. 4, At 11:15 A.M. Perfusion of dextran stopped for 3 minutes.



Fig. 3. 1, At 10:30 A.M. Optimal coronary back pressure of Dog No. of first group after occlusion of circumflex coronary artery. 2, At 10:41 A.M. Back pressure after 10 minutes of perfusion of venous blood. 3, At 9:15 A.M. Optimal coronary back pressure of Dog No. 5 of second group after occlusion of circumflex coronary artery. 4, At 9:30 A.M. Coronary back pressure after 10 minutes of dextran perfusion.

or were slightly lower The venous pressures decreased but did not reach the preocclusive level The average back pressure was slightly decreased Perfusion of low molecular dextran oxygenated or nonoxygenated at the same rates could maintain the aortic pressure at preocclusive or higher levels when exsanguination was not performed during perfusion When perfusion was stopped the back pressures could be recorded only after an elapse of 20 to 30 seconds when venous blood was perfused and 3 to 5 minutes when dextran was perfused

The *second subject* to be investigated was *the cardiac function when the perfusion of the circumflex coronary artery was initiated and maintained with low molecular weight dextran* or Tyrode solution at a higher flow rate of 25 ml per minute the starting perfusion flow being at lower or higher rates*

Methods

Fifteen unselected dogs which weighed between 14 5 and 16 2 kilograms were used *The circumflex coronary artery was cannulated* as before and back pressures were recorded These pressures were between 18 5 and 50 40 mm Hg Low molecular dextran at body temperature and at a rate of 25 ml per minute was then perfused in 10 dogs and Tyrode solution at the same rate in the other 5 The starting perfusion rates were 25 and 4 ml respectively the latter being increased to 25 ml within 2 minutes After 10 minutes of perfusion exsanguination was performed as before

Results

When the perfusion was started at a rate of 25 ml ventricular fibrillation occurred in 4 of 5 dogs in the dextran perfusion group and in 2 of 2 dogs in the Tyrode perfusion group In 2 of these dogs with fibrillating hearts after perfusion of dextran* the perfusion during heart massage and defibrillation was continued After 5 minutes of effort not only was defibrillation impossible but edema appeared on the left border and posterior surface of the left ventricle The perfusion was then stopped and heart massage was continued for 10 to 14 minutes after which defibrillation was possible However the contractions of the heart were weak and the systemic pressure could not be maintained at a level higher than 60/40 mm Hg The perfusion was started again* but the systemic pressure remained unchanged When phlebotomy was started the aortic pressure decreased still more the venous pressure increased 10 to 12 mm Hg and after 11 to 16 minutes of perfusion the heart stopped in diastole The weight of the immediately excised heart of these 2 dogs was 17 to 28 per cent higher than the calculated predicted weight In the other 4 dogs with fibrillating hearts the perfusion was stopped immediately After heart massage and defibrillation the heartbeat could easily be restored The perfusion was started again and continued at the same rates for 30 minutes After 10 minutes of perfusion exsanguination began as before The hemodynamic changes during perfusion were similar to those in the previous group In the group of 8 dogs in which the starting perfusion rate of dextran or Tyrode solution of 4 ml per minute was gradually increased to 25 ml within 2 minutes no fibrillation or other complication occurred during perfusion During the first 10 minutes of perfusion in 8 animals exsanguination was not performed The systemic pressure reached or exceeded the preocclusive level during perfusion time the venous pressure being increased 2 to 5 mm Hg When the perfusion was stopped every 10 minutes the backflow blood appeared in the cannula within 1 3 to 2 minutes when Tyrode solution was perfused and within 3 to 5 minutes when dextran was perfused (Fig 6) During this time the whitish area of the myocardium decreased significantly or even disappeared when Tyrode solution was perfused and remained unchanged or decreased slightly when dextran was perfused The systemic pressures began to decrease slightly when the perfusion of Tyrode solution was stopped during the measurements of backflow Against this the systemic pressure remained unchanged during the 3 to 5 minutes that the artery was not perfused with dextran The back pressures were 30/15 to 20/10 mm Hg when Tyrode solution was perfused and

*Molecular weight 40,000

*With 17 [illegible]

between 20/10 and 30/18 mm. Hg when dextran was perfused (Fig. 3). When after perfusion of 250 ml. exsanguination was started, the systemic pressure gradually decreased and after 30 minutes of perfusion-exsanguination the heart was still beating rhythmically, although the systemic pressures were at low levels. The temperature of the esophagus was decreased by 2.5 to 4° Celsius. After sacrifice of the dogs heart edema was not observed.

Summary of results. Abrupt perfusion of low molecular dextran or Tyrode solution into the circumflex coronary artery produced fibrillation in 6 of 7 animals when perfusion of venous blood at high levels of pressure was not previously taking place. The defibrillation was possible when the perfusion was stopped during fibrillation. However, when perfusion was continued edema of the heart occurred. In no instances did fibrillation occur when these perfusions were started at lower rates and gradually increased. The heartbeat and pressure could be kept at apparently normal levels during these perfusions. The back pressures could be stabilized and recorded within 1.3 to 5 minutes when the perfusion was stopped, depending on the viscosity of the perfused fluid and the initial level of back pressure.

The *third subject* to be investigated was *the cardiac function when the perfusion of low molecular dextran or Tyrode solution was started and maintained at low flow rates or 4 ml. per minute.*

Methods

Six dogs which weighed between 12 and 15.5 kilograms were used. The circumflex coronary artery was cannulated and back pressures were recorded. Low molecular dextran (in 3 dogs) and Tyrode solution (in the other 3) were infused at a rate of 4 ml. per minute.

Results

Ventricular fibrillation occurred during cannulation in one animal. The perfusion was stopped. The heartbeat was restored by instituting heart massage and defibrillation. Perfusion was then restarted, but the decreased arterial pressure after defibrillation could not be increased. During perfusion, fibrillation reappeared after 17 minutes. During the low rate of perfusion in the other 5 dogs the extrasystoles increased. The aortic pressures were slightly under the postocclusive levels. The venous pressures increased still more. After 17 to 20 minutes of perfusion, fibrillation occurred in all of the animals. The perfusion was then stopped; after heart massage and defibrillation the heartbeat could be restored, but the pressures were at a low level. Perfusion was then restarted with the same fluids and within 2 minutes the rate of perfusion was increased to 25 ml. per minute. Two to 4 minutes later the systemic pressure was increased gradually to near preocclusive levels (Fig. 4). After 10 to 20 minutes exsanguination was started, the perfusion being continued for an additional 20 minutes. The hemodynamic changes were the same as those which occurred in the previous group. Every 10 minutes the perfusion was stopped and back pressures were recorded (Fig. 6). The average time necessary to establish the back pressure records when dextran was perfused was 4 to 5 minutes from the moment that the perfusion was stopped and 1.5 to 2 minutes when Tyrode solution was perfused. The average back pressure was 24.8 mm. Hg. After these 30 minutes of perfusion-exsanguination the heart was still beating rhythmically, although the systemic arterial pressure gradually decreased. The animals were sacrificed. Heart edema was not observed.

Summary of results. Perfusion of low molecular dextran or Tyrode solution at low rates resulted in ventricular fibrillation within 20 minutes from the beginning of the perfusion. After defibrillation and gradual increase in the perfusion rate to 25 ml. per minute the systemic pressures could be restored and maintained near the preocclusive levels as long as exsanguination was not performed.

The *fourth subject* to be investigated was *the cardiac function during perfusion of isotonic glucose into the circumflex coronary artery at a flow rate of 25 ml. per minute.*

Methods

In 5 dogs which weighed between 13 and 15 kilograms and in which the angle of the bifurcation of the left coronary artery was supplied from branches of the anter

descending artery an isotonic solution of glucose at 37° was perfused. The perfusion was started at a rate of 4 ml. per minute and gradually increased to 25 ml. per minute within 2 minutes.

Results

After 3 to 5 minutes of perfusion, fibrillation occurred in all animals. The perfusion was stopped. Heart massage and defibrillation could restore the heartbeat. Low molecular dextran was then perfused at a rate of 25 ml. per minute for 5 minutes. During perfusion of dextran the aortic pressure increased to nearly the preocclusive level. After the 5 minutes of perfusion of dextran, perfusion of glucose was started again at the same rate as that for dextran. Within 3 to 6 minutes of perfusion, fibrillation occurred in all animals (Fig. 5).

Summary of results. Perfusion of 25 ml. of isotonic glucose per minute into the circumflex coronary artery resulted in ventricular fibrillation in all animals within 3 to 5 minutes. After defibrillation, perfusion of low molecular dextran at the same flow rate could maintain the heartbeat and pressure during the perfusion time. Reperfusion of glucose resulted again in fibrillation.

Control dogs were necessary in order *to compare the cardiac function and hemodynamics after 1 hour of occlusion and cannulation of the circumflex coronary artery with the several above-mentioned perfusions.*

Methods

Twenty-five control dogs which weighed between 13 and 20 kilograms were used. The circumflex coronary artery was occluded and cannulated by means of the same technique used before, and back pressures were recorded. Aortic and venacaval pressures were measured as before during 1 hour.

Results

During cannulation, ventricular fibrillation occurred in 6 dogs. The heartbeat could be restored by instituting heart massage and defibrillation, but the pressures remained decreased during the observation time. In 6 of the other 19 dogs the aortic pressure remained unchanged for 1 hour, although the venous pressure somehow increased. In the other animals the aortic pressure gradually decreased and the venous pressure increased. Ventricular fibrillation occurred during the first hour in 8 more of these dogs, in every case between the sixteenth and the sixtieth minutes after the occlusion.

Summary of results. In 25 control dogs occlusion of the circumflex coronary artery produced ventricular fibrillation within 1 hour in 8 dogs. During cannulation of the artery, fibrillation occurred in 6 more dogs. Defibrillation was possible although the artery was cannulated. In 6 dogs with initially high coronary retropressure, the postocclusive systemic arterial pressure remained unchanged during 1 hour of observation time.

Discussion

These experiments have confirmed again the conclusions of our previous investigations[1] which demonstrated that differences in oxygen tension in the nonischemic and perfused ischemic region of the left ventricular myocardium did not disturb the coordinated mechanism of the heartbeat. When the circumflex coronary artery supplying about 70 per cent of the muscle mass of the left ventricle was perfused with venous blood, low molecular dextran, or Tyrode solution, oxygenated or not, the normal heartbeat could be maintained and the pressures kept equal to or slightly below the preocclusive levels as long as hypervolemia resulting from the hyperperfusion or anemia from exsanguination did not occur. Comparing these results with those of perfusion of the anterior descending coronary artery,[1] we may make the following considerations. On the assumption that flow through the anterior descending coronary artery in the normal resting dog averages 1.17 ml. of blood per minute per gram of left ventricular muscle, and that flow through the circumflex artery averages about 1.26 ml. per gram of left ventricular muscle, in combination with the weight of the left ventricular myocardium, which has an average of 0.00315 of the body weight,[6] the flow in the two main branches of the left coronary artery of a healthy resting dog of 15 kilograms can be calculated thus: the flow through the anterior descending artery, which supplies 30 per

cent of left ventricular mass should be about 16.5 ml per minute whereas the flow through the circumflex coronary artery with a distribution of [illegible]0 per cent to the left ventricle should be about 41.6 ml per minute (the flow of the septal branch of the left coronary artery is not included in this calculation). It was surprising that perfusion not only of 25 ml of venous blood per minute at systemic pressures but also of low molecular dextran or Tyrode solution saturated with oxygen in one atmospheric pressure or not saturated could ensure an apparently *normal heart function during the time of perfusion*. What was the source of energy of the heart contraction during perfusion? If in the case of perfusion of venous blood this energy could be attributed to the oxygen in the venous blood with its 14 volumes content this explanation cannot be considered with the other perfusion fluids especially when they were not oxygenated. It might be suggested that the metabolites of the anoxic myocardial cells spread out to the coronary circulation from the perfused dextran or Tyrode solution could stimulate a local vasodilatation and opening of the intracoronary anastomoses thus increasing the local blood circulation. This suggestion can be rejected however because (a) the extreme myocardial pallor in the perfused area indicates that blood was washed out of the circumflex coronary area and (b) when after 10 minutes the dextran or Tyrode perfusion was stopped and back pressures were observed *we had to wait 3 to 5 minutes after* dextran and 1.3 to 2 minutes after Tyrode before noting the first traces of backflow blood or recording the first signs of the slowly appearing back pressures. Once blood failed to circulate sufficiently through the pale anoxic myocardium we must admit that the contractile strength of the circumflex area of the left ventricle was

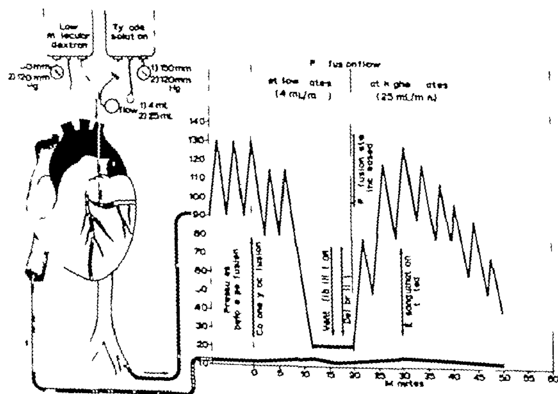


Fig. 4 Perfusion of low molecular dextran or Tyrode solution with flow rate of 4 ml per minute resulted in ventricular fibrillation. After defibrillation and re-perfusion of the same fluids with the flow gradually increased to 25 ml per minute the systemic pressures could be maintained near the preocclusive levels.

Fig. 3. Isotonic glucose solution perfused into circumflex coronary artery at a low rate which was gradually increased to 25 ml. per minute resulted in prompt ventricular fibrillation. After defibrillation, perfusion of low molecular dextran at the same rate of flow could maintain pressures near the preocclusive level. The perfusion of glucose again resulted in fibrillation.

maintained by the perfusion of Tyrode solution or even by the nonmetabolic dextran saline solution. It was remarkable that the pale area of myocardium revealed visually at least no decreased contraction or any region of systolic expansion. Although we have not performed myographical investigations on contraction in this area, the stable maintenance of an apparently normal heartbeat and systemic pressure during the different perfusions suggest at least a satisfactory myocardial contraction. We repeatedly observed that after the perfusion of Tyrode solution was stopped this whitish area began to decrease after 1.5 to 2 minutes because of inflow of the collateral blood. The arterial pressure then began gradually to decrease and the venous pressure to increase. Conversely, after the 10 minute perfusion of low molecular dextran was stopped the whitish area remained unchanged for 3.5 to 5 minutes while the pressures also remained unchanged. The decrease in systemic pressure which then began was much slower than when the perfusion of Tyrode solution was stopped. Similar results are reported after perfusing the coronary arteries of

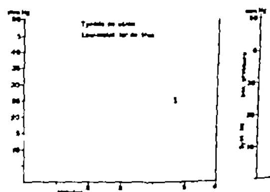


Fig. 4. Time necessary for establishment of circumflex coronary artery back pressures after 10 minutes of coronary perfusion in relation to viscosity of perfused fluid.

isolated hearts with the same nonmetabolic fluids[4] Recently it was reported[3] that when homologous serum was perfused in a main coronary artery the heart function was satisfactory also

It is known that in isolated perfused hearts the myocardium can utilize fats proteins and carbohydrates for metabolic needs and to obtain energy without requiring oxygen For example isolated hearts perfused with glucose can beat for 2 days and 13 hours[8 11] and intensively perfused isolated mammalian hearts can function for several hours[4] Isolated hearts in which the coronaries are perfused with gaseous oxygen can also beat up to 8 hours[5] The coronary perfusion of isolated hearts cannot be compared with the experiments in which perfusion supplies the heart muscle with the necessary energy to maintain the circulatory work load during the observation time It was interesting that perfusion of nonmetabolic fluids such as dextran in saline could maintain the circulation work load whereas perfusion of isotonic solutions of glucose resulted in a gradual decrease in the systemic pressure with ventricular fibrillation The perfused region then became edematous due to retention of glucose Such results have not been observed when glucose was perfused in the isolated heart for a much longer period of time[4] When low molecular dextran or Tyrode solution were perfused cardiac edema was not observed In repeated observations when the perfusion was stopped or the flow decreased contraction of the heart became weaker and the systemic pressure gradually decreased until the heart stopped in diastole or fibrillated These hemodynamic changes occurred more gradually and slowly when the perfused dextran was decreased or stopped and much more quickly when the Tyrode perfusion was decreased or stopped The explanation of these findings may be that the lower viscosity Tyrode solution could be removed more quickly from the capillaries than the low molecular dextran of higher viscosity From the foregoing we can conclude that the perfusion flow in coronary arteries is apparently the principal physiologic entity which regulates cardiac function in vivo These observations can perhaps be correlated with the hemodynamic results in 6 control dogs in which after occlusion of the circumflex coronary artery at its origin the systemic pressures remained unchanged during 1 hour of observation In each of these animals the back pressure of the occluded artery was maintained at high levels between 50 40 and 33 20 mm Hg In control animals in which after occlusion of the artery the function of the collaterals was probably inadequate the systemic pressure decreased the coronary back pressure was between 30 15 and 10 0 mm Hg These higher coronary retropressures indicate that the immediate function of the intracoronary collaterals is to ensure a good pressure and flow to the ischemic myocardial region resulting in an apparently satisfactory function and stabilization of the systemic pressures These particular hearts had a good contraction because of the appearance of newly functioning increased collaterals[1] In the other control animals in which the function of the collaterals was probably inadequate the coronary backflow was between 30 15 and 10 0 mm Hg In several we observed that the systemic arterial pressure decreased much quicker and that the venous pressure increased much more until hemodynamic failure occurred during the first hour These findings in our control animals reinforce the above mentioned suggestion that coronary artery retropressures appeared to have a significant value in cardiac performance The effects of coronary perfusion in those hearts with high postocclusive retropressure may be indifferent In the ischemic hearts with low retropressures evolving into hypodynamic failure perfusion distended the vessels of the ischemic area and stopped the inflow of collateral blood from the nonischemic region of the heart in this way reinforcing the vascularization of the pink area of the myocardium which has the function initially at least of maintaining the resistance of the circulation This hypothesis is suggested after the observation that in conditions of previously high coronary postocclusive retropressure when dextran was perfused for 10 minutes and the perfusion then stopped backflow blood reappeared in the perfusing cannula after about 3 minutes Conversely in conditions of lower retropressure when

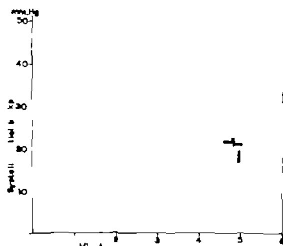


Fig. 7. Relation of initial level of postocclusive coronary back pressure to time of establishment of back pressures after 10 minutes of perfusion of the circumflex coronary artery with low molecular dextran.

the perfusion was stopped blood reappeared after about 5 minutes (Fig. 7). These differences were not clearly marked when the Tyrode solution was perfused. Conversely, the washing out of dextran with a molecular weight of 40,000 needed apparently much more time. These observations can also be compared with the fact that when the perfusion of dextran was stopped for 5 minutes the perfused area continued to be pale and the systemic *pressure remained almost unchanged.*

Another action of the perfused fluids is to wash metabolites out of the ischemic myocardial tissues. The fact that the viscosity of the low molecular dextran and Tyrode solution is lower than that of the collateral blood facilitates the easier penetration of these fluids to an extended area of the capillary bed. This penetration could also facilitate the immediate exchange of the small amount of diluted oxygen to the tissue fluid and the myocardial cell.

In conditions of low postocclusive coronary retropressure blood fails to circulate actively, a situation which predisposes to stagnation and aggregation of blood cells. This stagnation may gradually lead to microthrombosis,[11,14] which decreases still more the rate of blood flow, especially at low flow rates, as in venules and sinusoids. The ischemic myocardium then decreases its contractility, which further decreases the closure by compressing the capillaries between the myofibrillae, a situation which leads to still more extensive stagnation of the capillary blood. Not only does a reduction in the delivery of oxygen, oxidizable substances, and other nutrients occur, but there is also an impairment in the removal of carbon dioxide and the nitrogenous and acid end products of tissue metabolism. The rheological alterations in the stagnating blood in the ischemic region can be reversed when the occluded artery is perfused with low molecular dextran or Tyrode solution at high pressures. Perfusion of those fluids at low pressure was not effective. Our experiments have demonstrated consistently that the perfusion of nonoxygenated nonmetabolic fluids under high pressure can ensure much better heart *function than does stagnated collateral* blood which circulates in the ischemic myocardium under conditions of low retropressure.

The known observation that fibrillation may occur within 20 seconds after sudden release of the temporarily occluded coronary artery[17] was also found during the first few seconds of the different perfusions. When venous blood was initially perfused at high pressures fibrillation occurred in 28.6 per cent of the experiments. The level of coronary retropressure before perfusion *in the animals was low (average 20/5).* When the perfusion of venous blood was started at low pressure and flow (4 ml. per minute), fibrillation did not occur. Much more frequently fibrillation occurred at the moment at which perfusions of dextran or Tyrode solution were started when these perfusions were given at high pressure; when perfusion of these fluids began at lower pressures and flows (4 ml. per minute) and then was gradually increased within 2 minutes, fibrillation did not occur. When perfusion of dextran or Tyrode solution at high pressure and flows began just after a previous perfusion of venous blood, fibrillation did not occur. It was interesting to notice that in animals in which postocclusively there was high coronary retropressure (40/30 mm. Hg) fibrillation never occurred when the aforementioned *fluid were perfused at high* pressure. From those observations we may

conclude that perfusion in conditions of high retropressure do not produce fibrillation conversely perfusion in conditions of low retropressure do produce fibrillation

The difference in the results when isotonic glucose was perfused was very characteristic. Whenever glucose was perfused at the same rates fibrillation occurred within 1 to 4 minutes. When glucose was perfused after 5 minutes of perfusion of dextran total fibrillation was more delayed evidently because some time was necessary for the dextran to be washed out and for glucose to reach the capillary bed

From the foregoing we conclude that the decrease in oxygen content of the myocardium in the area of the circumflex artery can be compatible with life and apparently undisturbed heart function when venous blood low molecular dextran or Tyrode solution is perfused at high pressure through the circumflex coronary artery. Conversely when perfusion is maintained at low pressure hypodynamic changes gradually occur and fibrillation ensues. These experimental findings allow consideration of the clinical utility of the perfusion of low molecular weight dextran at the coronary ostium in cases of operation for repair of the aortic valve or for ascending aorta aneurysm or even of the perfusion of the coronary arteries during coronary endarterectomies or anastomoses

Summary

1 Perfusions of venous blood for 60 minutes at a rate of 25 ml per minute into the circumflex coronary artery did not alter significantly the rate of heartbeat nor the aortic or venous pressure. Perfusion of low molecular weight dextran after perfusion of venous blood at the same rates had similar effects as long as decompensating exsanguination was not performed

2 Perfusion of low molecular dextran or Tyrode solution at low rates resulted in fibrillation within 20 minutes. After defibrillation a gradual increase in the perfusion rate to 25 ml per minute could maintain the normal heartbeat and systemic pressures

3 When the starting rates of perfusion began at a high level fibrillation occurred especially when either low molecular dextran or Tyrode solution was perfused. In no instance did fibrillation occur when the perfusions were started at lower rates and then gradually increased to 25 ml per minute within 2 minutes

4 When during fibrillation after perfusion of dextran the perfusion was continued heart edema occurred. Defibrillation was possible when the perfusion was stopped

5 After the coronary perfusion with dextran or Tyrode solution was stopped a steady correlation was observed between the time of establishment of the back pressure the viscosity of the perfused fluid and the initial level of postocclusive back pressure

6 Perfusion of isotonic glucose solution at the same rates resulted in fibrillation. After defibrillation perfusion of low molecular dextran could maintain heartbeat and pressures. After re-perfusion of glucose fibrillation reappeared

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the mid la icular line The rhythm was irregular with many extra systoles Neurological examination was normal except for the presence of Hoffman sign bilaterally The remainder of the examination was unremarkable

Continuous ECG monitoring after her admission to the hospital revealed what appeared to be multifocal ventricular premature systoles She had one seizure during monitoring and the rhythm was described as gro ly irregular ventricular ectopic rhythm Unfortunately a permanent recording was not obtained at that time X ray films of the skull at the time of her admission were normal A chest X ray film disclosed fibronodular densities in both upper lung field suggestive of old granulomatous disease The heart was normal in size and configuration The spinal fluid was normal with no cells sugar was 100 mg per cent chloride 136 mEq protein 17 mg per cent a culture of spinal fluid was sterile Complete blood count and urinalysis were normal Sputum smears for acid fast bacilli and blood cultures were negative

Laboratory investigation on Aug 11 1963 showed that the calcium was 9 3 mg per cent phosphorus 4 6 mg per cent sodium 140 mEq /L potassium 3 7 mEq /L chloride 101 mEq /L CO 24 and pH (venous) 7 47 Serologic test for syphilis (V D R L) was negative Blood sugar was 80 mg per cent blood urea nitrogen 9 mg per cent and total protein 9 mg per cent On Aug 13 1963 the serum potassium was 4 4 mEq /L

The first glucose tolerance test on Aug 19 1963 revealed blood sugar of 66 mg per cent in 1 hour 0 in 2 hours and 60 in 3 hours When this test was repeated 2 da later the fasting blood sugar w 76 mg per cent the ½ hour sample 114 mg per cent the 1 hour sample 110 mg per cent and the 2 3 and 5 hour blood sugars were 90 60 and 80 mg per cent respectively

The electrocardiogram obtained on Aug 10 1963 (Fig 1) shows S-A rhythm with a P P interval of 0 77 second The sinus rhythm is interrupted by ventricular ectopic systole with a run of five such ectopic beats in Lead I and three in Lead II The P R and QRS intervals measured 0 16 and 0 08 second respectively It is difficult to determine with any degree of certainty the Q T interval because it fuses with the U waves An assumption made that in Lead V and V the notch separates the T and U waves and thus the Q T interval measures 0 44 second Prominent U waves are recorded in all leads with marked electrical alternation after ventricular premature systoles This alternation persist for a number of cycles after the ectopic beat thus suggesting at least partial independence from the preceding cycle length The tracing recorded on Aug 15 1963 (Fig 2) 5 days after admission shows no essential change except for lack of the negativity in Lead V After 700 mEq of potassium was given orally over a 10-hour period the U waves disappeared and the T wave assumed the tented appearance so frequently seen with hyperkalemia The Q-T was determined in Lead V_2 still measures 0 40 to 0 44 second (Fig 3 8 16 63)

The patient made an uneventful recovery and was discharged from the hospital on Aug 2 1963

Discussion

The seizures in this patient are typical of the cerebral anoxia which occurs when the cardiac output ceases abruptly due to ventricular tachycardia or standstill [11] The electrocardiogram did show runs of multifocal premature ventricular contractions which suggests that the mechanism of seizures was a ventricular arrhythmia The striking electrocardiographic feature was the large U waves with postextrasystolic alternation Potassium was determined on August 11 and 13 and as already indicated was 3 7 and 4 4 mEq per liter which is within normal limits for our laboratory However the ECG tracings recorded on August 10 and 15 showed a pronounced hypokalemic pattern It was only after the administration of oral potassium that all of these ECG abnormalities disappeared in fact a pattern of hyperkalemia appeared with prompt and complete cessation of the seizures It is reasonable to assume from the ECG changes after the administration of potassium that depletion of this cation contributed to the increased U wave amplitude the ventricular extrasystoles and the clinical state encountered in this patient The ECG findings in our case tend to support the fact that occasionally the cardiographic changes may be a poor index of the plasma level of potassium

The U wave and the T wave are thought to represent some phase of repolarization of the myocardium and usually have the same polarity [13,14] In general there is a parallel between the amplitudes of the T wave and the U wave i e when the T wave is tall the U wave also tends to be tall [14] In hypokalemia however this does not occur and the T wave decreases while the U wave increases in amplitude [1] In the present case the U waves were very much pronounced and approached in magnitude those seen with familial periodic paralysis [15]

A relationship seems to exist between the U wave and the occurrence of premature ventricular contractions Lepeschkin [13] has stated that with the exception of *quinidine those factors* which increase U wave amplitude also increase ventricular excitability and favor the occurrence of ventricular premature contractions The

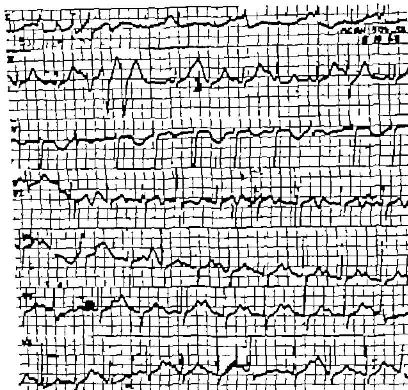


Fig. 1 The electrocardiogram on the day of admission shows sinus rhythm with premature ventricular systoles. Giant U waves and postextrasystolic U wave alternans. (See text.)

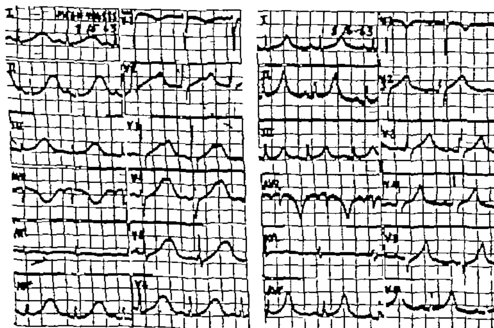


Fig. 2 The electrocardiogram on Aug. 15 1963 illustrate large U waves. On the following day the U waves disappeared and tented T waves appeared. (See text.)

negative after potentials responsible for the U wave may also be responsible for the supernormal phase of excitability It is during this interval that ventricular extrasystoles are likely to appear [15,17,18]

In our case we observed partial fusion between T and U waves in the sinus beat which followed the ventricular premature systole Lepeschkin[13] attributes this to the occurrence of prolongation of the Q T interval (with the Q U interval remaining stable) after a sudden long pause However in our case fusion of the T and U waves was *not caused by prolongation* of the Q T interval after a long pause since the apex of the T wave did not change during alternation whereas the amplitude of the U wave did change

A review of the literature on postextrasystolic T wave changes disclosed only two references to postextrasystolic U wave changes Levine and his co workers[5] noted that in rare instances postextrasystolic T wave and U wave changes occurred simultaneously They concluded that the U wave changes may constitute an integral part of the postextrasystolic changes A similar finding was reported by McLachlan[9] Both of these investigators implied that the postextrasystolic T wave and U wave changes have the same clinical significance and that both are indicative of myocardial disease [19,1] In our case we were unable to find any evidence of organic heart disease although an obscure form of myopathy cannot be ruled out

Summary

A case of postextrasystolic U wave alternans that most likely was due to depletion of potassium is presented and its significance is discussed

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Paradoxical acceleration of ventricular tachycardia after procaine amide therapy

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It has been over a decade since procaine amide was introduced for the treatment of cardiac arrhythmias. During this time numerous reports have attested to its effectiveness in the termination of ectopic rhythms, particularly those of ventricular origin.

Ventricular tachycardia may represent a medical emergency that requires immediate therapy directed toward abolition of the arrhythmia. As compared to quinidine, procaine amide is the drug of choice in terminating ventricular arrhythmias since it does not depress myocardial contractility and has fewer side effects when administered parenterally.[1]

We recently treated a patient with ventricular tachycardia by the administration of intravenous procaine amide. Prior to conversion to normal sinus rhythm there was a significant acceleration of the ventricular rate without any change in the ectopic focus or intraventricular conduction. To our knowledge such a phenomenon has never been recorded with procaine amide. The mechanism responsible for such a phenomenon, as well as its therapeutic implications, will be discussed.

Case report

A 60-year-old white man was well until the afternoon of Feb. 13, 1963, when he experienced the sudden onset of sharp retrosternal pain unrelated to exertion. There was no radiation of the pain. The patient denied dyspnea, diaphoresis, or palpitation.

He was seen by a private physician 8 hours prior to admission and was given four (200 mg.) quinidine tablets over two 4 hour period for a tachycardia. Because of persistent chest pain he came to the emergency room 4 hours after taking the last quinidine tablet.

Twelve years previously the patient had had a myocardial infarct. He had no cardiovascular symptoms since that time except for intermittent claudication which necessitated a bilateral lumbar sympathectomy in 1957 with considerable improvement. The patient was treated for a duodenal ulcer 1 year before admission. The remainder of the past history was not remarkable except for an inguinal herniorrhaphy in 195[illegible] and a ligation and stripping of varicose veins in 1959. He was not taking any cardiac or diuretic drugs prior to the onset of the present illness.

Physical examination. He was a well-nourished, well-developed man who lay comfortably in bed. The temperature was 101 F., the pulse was 1[illegible]0 per minute and regular, the blood pressure was 80/60 mm. Hg, and the respirations were 20 per minute. There was no cyanosis, dyspnea, or orthopnea. The neck veins were flat. Diffuse expiratory wheezes were present over the posterior chest. No rales were heard. The heart was not enlarged. There was

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Fig 1 A Lead II reveal a tachycardia with a ventricular rate of 167 per min ut There are no ible P wa es B Esophageal lead confirms the presence of entricular tachycardia (atrial rate of 88 per minute and entricular rate of 167 per minute)



Fig 2 A Lead II at beginning of adminis tration of procaine amide (entricular rate of 167 per minute) B Lead II at 3 minutes Patient has received 300 mg of procaine amide (entricular rate of 215 per min te) C Second lat r the ECG reveal normal inus rhythm Note Q wa e of old po terior wall infarction

ariation in the inten ity of the fir t heart sound t the pex There was no audible murmur rub or gallop The remainder of the examination wa within normal limit

Diagnostic tudies at the time of dmi ion were follow enou pressure of 95 mm H_2O with a rise to 170 mm on compre sion of the right upper quadrant cir ulation time (arm to tongue) 17 second hematocrit 47 per cent wh te blood cell count 8 700 per cubic millimeter with normal dif ferential blood urea nitrogen 16 mg per cent urinal si and serum electrol tes normal SGOT 34 units A hest x ray film was normal

The electrocardiogram on admi ion (Fig 1 A) revealed a tach cardia w th a rat of 167 per minute There were no ible P waves Carotid inu pres ure ocular compression and stimulation of the gag refle had no effect on the arrhythmia Intra enou Neo-Synephrine produced a rise in the sy tolic pres ure to 160 mm Hg without con erting the arrhythmia Because of hyp ten ion an tra nou infu ion of metaraminol (Aramine) w s begun in rder to maintain the y t l pre ure t 100 mm Hg An esophageal lead (Fig 1 B) c nfirmed the pres e of ventricul r tachycardia During thi time the patient recei ed a ther 200 mg of quinidine

During the next 8 hours the patie t s systolic blood pres ure remained stable (at 90 to 100 mm Hg) without asopressors and the infu ion of meta raminol was replaced with 5 per cent dextrose in water Approximately 1 hour later w th monitoring by serial electrocardiographic tracing and blood pressure recording procaine amide (Pronestyl) wa injected intra enou l through the tubing at a rate of 100 mg (1 c.c) per minute (Fig)

After 3 minutes when the patient had received a total of 300 mg of procaine amide the electro cardiogram (Fig 2 B) revealed an acceleration of the entricular rate to 215 per minute without any change in the configuration or duration of the QRS wa Second later the patient rrhythmia reverted to normal sinus rhythm (Fig 2 C) There was no change in blood pressure during the period of conversion After normal sinus rhythm had been restored the patient w s placed on maintenance oral therapy w th procai ne amide Hi blood pres ure remained table at 110/70 mm Hg Serial electrocardiograms and determinations of t an aminase revealed no evidence of recent myocardial infarction The remainder of the hospital course w uneventful and he was di charged 2½ weeks after adm ion

Discussion

The cardiac effects of procaine amide are qualitatively similar to those of quinidine Conduction in cardiac muscle is delayed although to a different degree in the atrium ventricle and the bundle of His The effect is most pronounced at the A V node which suggests greater sen itivity of this ti sue to the drug The refractory period is prolonged the atrium being more affected than the ventricle In contra t to the depressant action of quinidine con tractility of the heart is usually not af fected by procaine amide Myocardial excitability to electrical stimulation i

depressed, this is more marked in the ventricle than in the atrium. Since high doses of procaine amide sometimes accelerate the sinus rate in the absence of an arrhythmia, an anticholinergic effect has been postulated.

When one considers the pharmacologic actions of procaine amide on the heart, there are several mechanisms whereby acceleration of a ventricular tachycardia may be explained. Although procaine amide may induce a tachycardia in the presence of normal sinus rhythm, it is conceivable that in our case of ventricular tachycardia the ectopic focus received parasympathetic innervation via the vagus nerve. Vagal fibers have never been conclusively shown to innervate the ventricular musculature. However, Dworkin[4] recently described a patient with frequent premature ventricular contractions (who was not taking any cardiac drugs) in whom carotid sinus pressure produced *complete* abolition of all premature ventricular contractions for the duration of carotid sinus massage. Three minutes after carotid *compression* the premature ventricular contractions returned at their *original* frequency. Although compression of the carotid sinus may inhibit sympathetic impulses to the ventricles, the known parasympathetic effects *of such a maneuver* suggest vagal innervation of the ventricular myocardium. *If such be the case*, the anticholinergic effect of procaine amide would explain acceleration of an ectopic ventricular focus.

Further evidence of vagal innervation of the ventricular myocardium is found in the work of Schwartz and de Sola Pool on patients with established atrioventricular dissociation. To summarize their results, the intravenous administration of atropine sulfate (grain 1/30) resulted in (1) a transitory slowing followed by a transitory acceleration of the idioventricular rate, (2) the disappearance of spontaneously developing premature beats of the ventricle, and (3) changes in the site of the idioventricular pacemaker from one of the bundles to the supraventricular portion of the A-V node. These effects of atropine sulfate strongly suggest that the idioventricular pacemaker is under the influence of the vagus nerve.

The efficacy of vasopressor drugs in terminating tachycardias of supraventricular origin, presumably via the carotid sinus mechanism with increased vagal tone to the heart, is well established. That vagal innervation of the ventricular myocardium may exist is suggested by the report of Greenspan and Shahgoldian,[5] who treated 3 patients with ventricular tachycardia by intravenous vasopressor drugs. Restoration of normal rhythm was achieved in all 3 patients. However, in one of their patients with acute myocardial infarction and shock, intravenous metaraminol terminated the ventricular tachycardia despite continued hypotension. This would imply a direct action on the myocardium rather than a secondary effect due to an elevation in the systemic blood pressure.

Denney and co-workers[6] presented a case of ventricular tachycardia treated with procaine amide in which progressive widening and notching of the QRS wave occurred, followed by a short paroxysm of ventricular acceleration of a prefibrillation type. Normal rhythm was restored upon cessation of procaine amide therapy. They postulated that the mechanism of re-entry excitation was responsible for the acceleration of the ventricular rate. However, in our patient there was no significant widening of the QRS wave nor change in its configuration (QRS = 0.18 to 0.20 sec. at a ventricular rate of 167 per minute and QRS = 0.20 sec. at a ventricular rate of 215 per minute).

Finally, a mechanism completely unrelated to the administration of procaine amide may be postulated to account for acceleration of a ventricular tachycardia. It has been amply demonstrated that any disturbance of cardiac rhythm may adversely influence systemic blood pressure, coronary blood flow, and myocardial metabolism. The severity of the effects in these areas depends on the site of origin, type, rate, and duration of the arrhythmia and the degree of underlying heart disease. In the presence of ventricular tachycardia the work of the heart is increased, which results in increased nutritional requirements. However, the arrhythmia itself causes impaired ventricular filling and output, with a fall in systemic

blood pressure and coronary perfusion The resulting myocardial ischemia with impaired myocardial metabolism not only perpetuates but could conceivably accelerate the arrhythmia although the latter has never been reported

Conclusions

Although it cannot be stated with certainty what mechanisms are responsible for acceleration of a ventricular tachycardia treated with procaine amide we do not think that this phenomenon represents a toxic manifestation of the drug The dose given was well within the accepted therapeutic range and the electrocardiogram showed no change in the duration or configuration of the QRS complex

In the treatment of ventricular tachycardia with procaine amide or quinidine most authorities recommend continuous treatment until normal rhythm is restored or toxic side effects appear the latter being most evident as electrocardiographic abnormalities or hypotension As evidenced by the restoration of normal sinus rhythm in our case one may judiciously administer procaine amide in the presence of ventricular tachycardia with acceleration of the ventricular rate provided that careful surveillance of the patient is maintained by continuous recording of the electrocardiograms for *widening* of the QRS complex and by frequent determinations of blood pressure

Summary

A case of ventricular tachycardia not associated with clinical myocardial infarction was treated with intravenous procaine amide Prior to conversion to normal sinus rhythm a significant acceleration of the ventricular rate in the absence of any intraventricular conduction defect occurred To our knowledge such a phenomenon has not been reported previously Several mechanisms were postulated to explain the pathophysiology of the increased ventricular rate It was suggested that such an event does not contraindicate further administration of the drug provided that the patient is closely monitored by the frequent recording of electrocardiograms and determinations of blood pressure

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Myotonia dystrophica with A-V dissociation and Stokes-Adams attacks

A case report and review of the literature

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Cardiac arrhythmias and conduction defects are often noted in patients with myotonia dystrophica. Documented cases of complete atrioventricular dissociation with Stokes-Adams attacks are rare. Litchfield[1] described the case of one patient who died from this complication.

The etiology of the rhythm disturbances and conduction defects has been controversial. Waring and associates[2] suggested that these changes were due to associated coronary atherosclerosis. Fisch and Evans[3] and De Wind and Jones[4] have presented evidence suggesting that these changes may be due to primary myocardial disease.

We recently treated a patient with myotonia dystrophica with Stokes-Adams syndrome due to complete A-V dissociation. An implantable electronic pacemaker was used in the management, providing us with an opportunity to examine the coronary arteries and obtain a myocardial biopsy.

Case history

This 50-year-old white married woman was admitted to the University of Kansas Medical Center on June 27, 1963. She had been in her [illegible] state of health until 3 weeks prior to admission, at which time she first began to experience dizziness when standing. Twelve days prior to admission, on June 15, 1963, she experienced two syncopal episodes which were accompanied by grand mal convulsions and urinary incontinence. She was taken to the emergency room of another hospital and found to have a pulse rate of 20. While in the emergency room, she had two more convulsive episodes, but experienced no further difficulty until she was admitted to the University of Kansas Medical Center for further evaluation.

She denied having dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, chest pain, or edema. However, for 4 years she had noted progressive weakness of the lower extremities and a nasal quality to her speech. Her 48-year-old brother, a paternal aunt, and a paternal uncle were all known to have myotonia dystrophica.

Her past history was noncontributory, except that a hysterectomy and bilateral oophorectomy had been performed when she was 38 years old.

On physical examination, she appeared to be quite pale. Her height was 61 inches and her weight was 96 pounds. She was alert, cooperative, and well oriented, but spoke with a nasal speech. A myopathic facies with receding hairline was noted. The pupils reacted to light and accommodation. No cataracts were noted. A few moist basilar rales were present. The abdomen was distended, but no organs were palpated. There was some muscle atrophy of the lower extremities. Neurological examination was negative. A myotonic response was elicited from the thumb. The heart was not enlarged to percussion. The first heart sound [illegible] intensity. The second heart sound was paradoxi

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Fig. 1. The ECG shows complete A-V dissociation. The atrial rate is 120/min. and the ventricular rate is 66/min. Ventricular complexes have the appearance of a left bundle branch block.

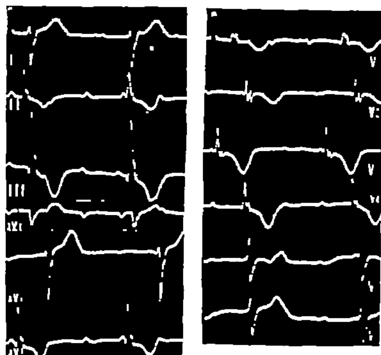


Fig. 2. The ECG shows complete A-V dissociation with an atrial rate of 100/min. and a ventricular rate of 31/min. The ventricular complexes in the present tracing have the appearance of those of right bundle branch block, compatible with an idioventricular pacemaker in the left ventricle, which is opposite to the focus in Fig. 1.

cally plit Atrial sound were heard A Grade 2 systolic ejection murmur was heard at the lower left sternal border

At the time of admission the blood count haematocrit urinalysis sedimentation rate serology blood urea nitrogen blood sugar electrolytes SGOT total and fractional protein bilirubin and alkaline phosphatase were all within normal limits The serum cholesterol was 278 mg per cent and the total blood lipid was 773 mg per cent Electromyographic studies confirmed the diagnosis of myotonia dystrophica The electrocardiogram (Fig 1) showed A V dissociation with the ventricular complexes having the appearance of those of left bundle branch block The atrial rate was 120 per minute and the ventricular rate was about 66 per minute and irregular

She was placed in an intensive-care unit where her heart rate and rhythm were continuously monitored by an electronic cardiac monitor Twelve hours after admission she developed ventricular fibrillation External cardiac massage and artificial respiration were initiated within 2 minutes and the patient was defibrillated by 600 volt A C shock Prior to defibrillation she became comatose and remained unresponsive after her heart was defibrillated The pupils were dilated and did not respond to light An electrode catheter was passed into the right ventricular outflow tract and was used to pace the heart at a rate of 75 per minute Respiration was maintained by an artificial respirator

She remained comatose and after 12 hours the catheter electrode and artificial respirator were withdrawn She was given hydrocortisone 50 mg intramuscularly every 6 hours Intravenous fluid were given for supportive therapy For the next 72 hours she remained stuporous responding only by withdrawal from painful stimuli After this her sensorium gradually cleared and her motor activity gradually returned By July 5 (7 days after cardiac arrest) she was able to sit in bed and feed herself There were no focal neurological defects but marked impairment of memory was noted On July 8 she experienced another Stokes Adams attack from which she recovered without incident After this she was given isoproterenol 5 mg sublingually four times daily

She was discharged from the hospital on July 17 1963 at which time she was ambulant able to read and moderately alert Her speech was occasionally inappropriate and a marked impairment of memory was noted Her electrocardiogram continued to show complete A V dissociation She was seen as an outpatient on July 31 at which time she showed a marked improvement in her mental status Her rehospitalization was prompted by a syncopal episode on Aug ? 1963 The electrocardiogram (Fig ?) showed complete A V dissociation with an atrial rate of 100 per minute and a ventricular rate of 34 per minute The ventricular complexes had the appearance of those of right bundle branch block compatible with an idioventricular pacemaker the left ventricle

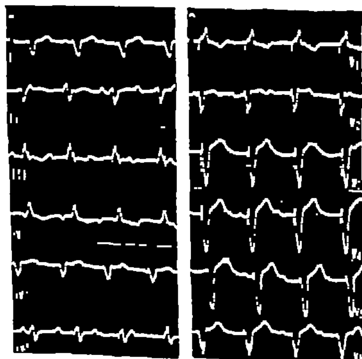


Fig 3 The ECG shows complete A V dissociation with an atrial rate of 94/min and a ventricular rate of 75/min Each ventricular complex is preceded by an electrical impulse from the implanted pacemaker

On August 3, with the patient under general endotracheal anesthesia, a left thoracotomy was performed. Direct inspection by palpation did not reveal evidence of gross coronary atherosclerosis. A Chardack-Greatbatch pacemaker was implanted in the left ventricle near the apex. After implantation of the electrodes, a small segment of myocardium was obtained (2 by 4 cm.) from the tip of the left ventricle.

Seven days postoperatively, it was noted that a segment of skin overlying the power pack was ischemic. She was returned to the operating room on the fourteenth postoperative day, at which time the power pack was moved to another site and a small flap fashioned to close the original wound. Convalescence was uneventful, and she was dismissed from the hospital on the twenty-first postoperative day, at which time the electrocardiogram (Fig. 3) showed complete A-V dissociation with an atrial rate of 94 per minute and a ventricular rate of 75 per minute. Each ventricular complex was preceded by an electrical impulse from the pacemaker. The ventricular complexes had the appearance of those of right bundle branch block.

She was last evaluated on Nov. 19, 1963, at which time she was caring for herself, doing light housework and cooking. A minimal memory defect persisted.

Biopsy findings. The myocardial biopsy (Fig. 4) showed individual muscle bundles separated by loose connective tissue in excess of the normal stroma. Lymphocytes and macrophages were predominant in the stroma. No area of dense massive scarring was noted. The muscle fibers had rather indistinct borders, a feathery cytoplasm with swelling, and longitudinal separation of myofibrils (Fig. 4). The nuclei were well preserved. The stroma was moderately cellular and contained lymphocytes, macrophages, and fibroblasts. Sections stained with crystal violet and Congo red showed no amyloid-like substance. PAS stain revealed many lipofuscin granules in the myocardial fibers, but also in a number of macrophages of the stroma, suggesting that some myocardial fibers had disintegrated. The iron stains for the same pigment were negative.

Discussion

Myotonia dystrophica is a hereditary disease of the neuromuscular junction described by Steinert[6] in 1909. It is characterized by the myotonic reaction of the muscles, dystrophy of the facial and neck muscles as well as the muscles of the lower extremities. Cataracts, frontal baldness, and sterility are other common findings. In 1911, Griffith first called attention to bradycardia in a patient with myotonia dystrophica. Distant heart sounds, splitting of the first sound, low blood pressure, and apical systolic murmurs have been re-

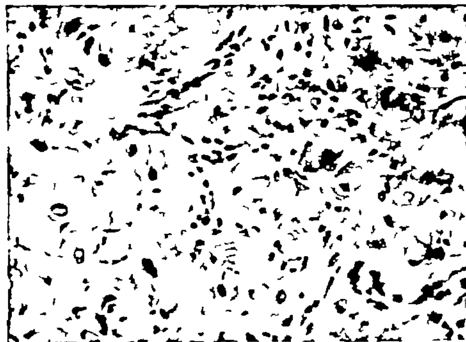


Fig. 4. Myocardial biopsy. Hematoxylin and eosin stain. ×250. This high-power photomicrograph shows the myocardial muscle fibers to have rather indistinct borders and a feathery cytoplasm with swelling and longitudinal separation of myofibrils. The nuclei are well preserved. The stroma is moderately cellular and contains lymphocytes, macrophages, and fibroblasts.

ported in patients with myotonia dystrophica.[1,2] Fisch[5] reviewed the electrocardiographic changes in 85 patients with myotonia dystrophica and found first-degree heart block, prolonged QRS duration, and transient atrial flutter or fibrillation as the most common disturbances. Only 2 patients had second-degree block.

Electrocardiographic changes such as isolated left axis deviation[7] and left bundle branch block[10] have been reported in patients with myotonia dystrophica before the changes in the skeletal muscle became evident. Davies and Evans[1] believed that patients with left axis deviation with deep S waves in Leads II and III had a fault within the myocardium in the anterolateral aspect of the left ventricle. They suggested that this abnormal pattern was due to diffuse myocardial scarring. Spurney and Wolf[6] reported the case of one patient who had had paroxysmal atrial flutter for 5 years before the skeletal muscular findings of myotonia became evident.

Although 85 per cent of the patients with myotonia dystrophica have abnormal electrocardiograms, there are only a few reports of A-V dissociation with Stokes-Adams attacks.[8] Litchfield[3] reported on one patient with myotonia dystrophica who developed A-V dissociation with Stokes-Adams attacks and subsequently died. An autopsy was not obtained. De Wind and Jones[4] found only 3 cases of complete heart block in 98 reported cases with electrocardiographic abnormalities.

The reason for the cardiac changes in myotonia dystrophica is unknown. The electrocardiographic abnormalities have been attributed to associated atherosclerosis.[2] If this were the case, a higher incidence of electrocardiographic abnormalities would be expected in the older age groups. De Wind and Jones,[4] reviewing 98 cases of myotonia dystrophica, found that the electrocardiographic abnormalities were as frequent in patients under 45 years of age as in those over 45 years of age. They thought that this would exclude atherosclerosis as the prime cause for the electrocardiographic changes. Payne and Greenfield[9] found a similar distribution of electrocardiographic abnormalities in their small series of patients and reached a similar conclusion. The electrocardiographic changes have also been attributed to prolonged vagal stimulation and quinine therapy, but this has not been substantiated clinically.[4]

The myocardium may be involved in the same degenerative process as the skeletal muscle, but the cardiac changes do not necessarily parallel the changes in skeletal muscle. Atrophy of myocardial fibers and variation in the size and shape of the myocardial nuclei were reported by Black and Ravin.[11] In 1954, Fisch and Evans[5] reported the autopsy findings in a patient with myotonia dystrophica. The heart showed diffuse fibrosis and separation of myocardial fibers by dense fibrous tissue. Hypertrophied muscle fibers and rectangular nuclei were also noted. The coronary arteries were not atherosclerotic. Although these histologic changes are not pathognomonic of myotonia dystrophica, they have been observed in several autopsied cases as well as in the myocardial biopsy obtained in this case. Since there was no appreciable coronary atherosclerosis, these nonspecific changes may have been due to the same pathologic process which involved the skeletal muscle. It is possible that these histologic changes may be responsible for the arrhythmias and conduction defects which in turn may cause the sudden unexpected deaths in patients with myotonia dystrophica.

Summary

The case of a patient with myotonia dystrophica who developed atrioventricular dissociation with Stokes-Adams attacks has been presented. Since the Stokes-Adams attacks were refractory to medical management, an implantable electronic pacemaker was utilized. This offered an opportunity to inspect the heart and obtain a biopsy, which showed diffuse fibrosis in the absence of gross coronary artery disease. These findings lend credence to the concept that the myocardial changes in myotonia dystrophica are not due to associated coronary artery disease.

We are indebted to Dr. Ronald Youmans for the electromyograph studies and to Dr. John Kepes for the histologic studies and interpretation of the biopsy material.

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Veins and venous tone

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The cardiovascular system has many facets each of which may spellbind an investigator. Thus, to a cardiologist it consists of the *Heart*, to which there happens to be connected a system of tubes justified mainly because it allows the output to return to the heart. To the expert on peripheral circulation it consists of a fascinating system of tubes for flow studies wherein incidentally the pressure head is said to have something to do with the heart. Again, to the investigator who is biophysically minded it is an inexhaustible source for the creation of stunning formulae of profound beauty and doubtful applicability. Lastly, to the expert on capillaries it is a vast and delicate exchange membrane which unfortunately has to be connected to other, far duller cardiovascular sections for providing the flow needed to put the all-important exchange into action. The only common denominator of these superspecialists would probably be their raised eyebrows if someone dared to suggest that the veins might be important too. However, such a vein enthusiast has indeed very good reasons for his suggestions, as will be discussed below.

These slightly caricatured specialist viewpoints are all somewhat out of focus, but in a way the expert on capillaries may claim to be less far away from the truth than the others. This is because after all it is across the capillary walls that the key function of the circulation—the establishment of a dynamic contact between the external and internal environment—is made possible by the maintenance of a capillary blood flow. Ultimately, all other cardiovascular compartments serve to adjust this capillary flow to a level adequate for establishing tissue homeostasis. However, it is equally true that if any of these other regulatory cardiovascular compartments should fail, the whole performance of the circulatory system would rapidly deteriorate. Indeed this would also be the consequence if the veins failed, although admittedly, to please the cardiologists, more quickly if the pump failed.

However, it must be admitted at once that the function and control of the venous system has been very little studied and understood even up to this very day. In evaluating to what extent cardiovascular researchers have since Harvey's days paid attention to venous function as compared with other aspects, one can only conclude that the negligence has been monumental and that the physiologists are mainly to blame. Yet one of William Harvey's most outstanding pupils, Richard Lower, appears to have had a surprisingly good grasp of the veins and their function, realizing their profound importance in cardiovascular performance in connection, for example, with changes in their tone

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or upon exposure to hydrostatic factors. Now and then during the subsequent centuries excellent studies dealing with one aspect or another of venous function have appeared, but they are indeed rare flowers on the now enormous tree of cardiovascular research grown during the course of the last three centuries.

Most investigators seem to have shuddered at the thought of studying the veins, and here methodological difficulties, real or imagined, must have played a dominating role. Presumably, this has tended to create a "sour grape" attitude, and hence a perpetuated negligence, now and then possibly stirred by vague feelings of bad conscience. On the other hand, intense effort has been devoted to such aspects as the function and control of the heart, the Windkessel function of the arteries, the regulation of the flow resistance and the blood pressure, etc. The early investigators certainly believed that the capillaries also deserved much attention, but these were apparently often considered to be too difficult to study. However, at this point the interest in the functionally different cardiovascular sections generally seemed to have reached its limit. To exaggerate a little, the veins were too often considered as admittedly necessary but certainly dull draining pipes deserving medical attention mainly as suitable places for taking samples or for giving drugs. It is in fact only during the last few decades that it has been more generally realized that venous function is indeed so important in cardiovascular performance that it deserves much more intensified research efforts.

For the discussion of the functional significance and the control of the veins, it might be advantageous to give some simple introductory definitions bearing on the functional differentiation of the cardiovascular system. We owe to William Harvey the great discovery that the flow of blood proceeds along two main circuits coupled in series to form a closed system, the pulmonary one for the direct contact with the external environment, and the systemic one for contact with the tissues, the two being perfused by the *right and the left* sides of the heart, respectively.

Although the systemic circulation consists of a great number of parallel-coupled vascular circuits differentiated to suit the demands of their particular tissues, the pulmonary vascular bed is in this respect fairly homogeneous. However, each individual circuit, pulmonary or systemic, can in turn be divided into a number of series-coupled, functionally differentiated sections which may be labeled *the pump, the Windkessel vessels, the resistance vessels, the sphincter vessels, the exchange vessels* (i.e., the true capillaries), *the shunt vessels* (present in some tissues only), and last but not least *the capacitance vessels*, connected to the filling side of the other half of the pump. These functionally based definitions (for detail see Folkow[1] and Mellander) do not however coincide exactly with the morphologically delineated sections. For instance, the resistance vessels comprise a major precapillary section (small arteries, arterioles, etc.) and a minor postcapillary section (venules and small veins). The capacitance vessels do largely correspond to the venous sections of the systemic and pulmonary circuits, but not entirely, because the heart itself and also the other vascular sections subserve a capacitance function to some extent. In any case, this makes it quite clear that the venous system must be of great importance in cardiovascular performance, both in contributing to the *resistance function* and in being a dominating element in the *capacitance function*.

If we consider first the *resistance function* of the veins, their quantitative contribution to flow resistance is quite small compared with the precapillary resistance section. However, in this particular case functional importance can by no means be evaluated only in terms of magnitude. It is important to realize that the capillaries are situated between two variable resistance sections that can be adjusted by means of their smooth muscles. The cardiovascular system is so designed that arterial and central venous pressures are normally maintained at fairly constant levels. Therefore, variations in blood flow will be primarily due to changes in the total resistance of the vascular bed, whereas adjustments of capillary mean hydrostatic pressure will depend upon changes in the

ratio between the precapillary and post capillary resistances This latter fact must not be forgotten since beside the nutritionally all important *diffusion exchange* a *filtration exchange* also occurs across the capillary walls This in turn is to a great extent responsible for the important partition of fluid between the extravascular and intravascular spaces Thus if the ratio of precapillary to postcapillary resistance is increased mean capillary hydrostatic pressure will fall leading to a net absorption of extravascular fluid to the circulation and vice versa to outward filtration when the ratio is decreased Changes in this ratio can be expected therefore to constitute one of the main physiologic variables in the filtration exchange and such changes can be brought about by appropriate adjustments of the smooth muscle activity within the two resistance compartments In altering this highly important ratio it is obvious that the denominator the venous resistance may theoretically exercise as equally profound an influence as the numerator the precapillary resistance hence the great potential importance of the veins also in the *resistance function* of the vascular bed

Furthermore the venous system is of dominant importance for the *capacitance function* of the circulatory system largely because it contains some 65 to 75 per cent of the entire blood volume[33] At the same time that it forms the indispensable return route from the capillary section to the heart it constitutes a voluminous and highly variable blood reservoir or cardiac forechamber It normally appears to be very exactly regulated to meet these demands even minor adjustments can profoundly affect the filling and thus the output of the pump In their capacitance function the veins of the *different* circuits subserve as a unit the cardiovascular system *as a whole* rather than any local needs of their particular tissues

It is for instance by reflex increases in venous tone that a promptly acting and in acute situations very adequate compensation for loss of blood can be achieved This capacitance response of the veins can thus be said to form a first line of defense acting in synergism with a pump adjustment for maintaining an adequate supply of blood to the tissues As a second line of defense to combat loss of fluid from the circulatory system concomitant adjustments of the precapillary to postcapillary resistance ratio may be mentioned When this ratio is increased a mobilization of tissue fluid into the vascular compartment will ensue a more slowly acting but nevertheless most important compensatory mechanism In this type of adjustment the veins are engaged in their role of postcapillary resistance vessels and such a regulation also serves the cardiovascular system *as a whole* rather than the immediate local tissue demands An important third line of defense against loss of fluid from the circulation is of course constituted by the renal conservation of fluid but this type of compensation is beyond the scope of the present survey

It is to be expected that the venous system with its above mentioned two main functions serving the circulatory system as a whole will demand a centrally integrated control for satisfactory performance and that only minimal interference by local regulatory mechanisms can be tolerated

In approaching the problem of how the venous system is in principle controlled under normal circumstances one has to take into consideration (a) the functional characteristics of its smooth muscles (b) the superimposed nervous and hormonal influences (c) its reflex and central control and also (d) the cooperation versus competition between neurogenic mechanisms and local factors which influence venous tone Our knowledge in this field is still fragmentary to a great extent because the venous system really is difficult to study at least in *quantitative* terms However quantitative studies are indeed required for a full understanding of the integrated function of the veins Scattered information obtained from studies using different techniques in many laboratories during the last few decades may permit some generalizations concerning the main principles of venous control How this control may subserve the cardiovascular system as a whole with regard to the regulation of total blood volume the distribution of available blood volume the

adjustment of venous return, etc., will be briefly outlined here. No comprehensive review of all the previous literature in the field will, however, be given; for a more complete reference list the reader is referred to other papers.[4,9]

In general, the control of any cardiovascular section tends to be organized at different levels, more and more complexly built extrinsic mechanisms being superimposed on the local factors. The very basis for functional differentiation is, of course, the special design characteristics of the different cardiovascular sections, which in general terms are well fitted for the functional demands made upon them. This general principle is certainly true also for the veins. Their thin distensible walls and wide-bore dimensions with consequent low resistance and large *volume make them well suited for their* capacitance function and their special task in resistance control. It is true that the great distensibility of the veins has considerable drawbacks in some respects, notably in man because of his erect posture, in which case the largest fraction of the venous system is situated below the level of the heart and is exposed to considerable hydrostatic forces, with consequent risks of the pooling of large amounts of blood, thus interfering with venous return. Man's special situation in this respect is, however, an exception rather than the rule within the animal kingdom, since in the majority of species the heart is placed fairly low in relation to the greater part of the venous system so that hydrostatic factors thus only slightly impair venous return. But, as will be discussed below, fairly effective countermeasures have been developed so that even in man venous return is not too badly impaired in this respect.

The vascular smooth muscle, as regard their basic characteristics, are evidently not always functionally uniform, independent of their location within the vascular bed. In fact, a considerable differentiation—more quantitative than qualitative in nature—seem to have taken place between the various vascular sections. Smooth muscles often exhibit automaticity, a myogenic tone, which let us first briefly consider as to its extent and location within the vascular bed. To particularize, an evaluation of its extent within the consecutive vascular sections of one and the same circuit shows that it seems to become gradually more dominant the closer the approach to the capillary level. This inherent smooth muscle activity appears, in fact, to be concentrated mainly in the small *precapillary resistance vessels* and, to a definite although hemodynamically less significant extent, also in the smallest postcapillary vessels (venules).[10] Let us start, therefore, at the "wrong end" and first deal briefly with some principles of the control of the resistance vessels because in many respects it is, for example, a contrast to that of the capacitance vessels. It appears that the very basis of the actively maintained flow resistance is a consequence of such an inherent smooth muscle activity. It establishes a *basal vascular tone*, which in general seems to be more pronounced the wider the range is between the resting and the maximal metabolic demands of the particular tissue. This locally established resistance tone creates a kind of "blood flow reserve," which is easily mobilized whenever accumulation of so-called vasodilator metabolites inhibits the vascular smooth muscles.[11]

Additionally, in most circuits the myogenic activity of the resistance vessels can be more or less strongly reinforced by the action of centrally controlled constrictor fibers. However, in the intact resting organism it seems as though the normally very low vasoconstrictor fiber discharge, as compared to the myogenic activity, contributes fairly little to the *total* flow resistance. Otherwise it is difficult to explain why the flow resistance in the major parallel-coupled circuits decreases fairly little, virtually not at all in some circuits, when their vessels are acutely deprived of their constrictor fiber influence, provided that factors such as the pressure head are kept essentially unchanged.[1] The addition of vasodilator drugs or metabolites, on the other hand, can in certain of these circuits produce a profound fall in their flow resistance. Such a principle of a primarily local control of the resistance vessels in most systemic circuits seems to be fairly logical since these vessels mainly subserve the nutritional blood supply of

the tissues. This by no means denies the fact that in states of emergency the superimposed constrictor fiber influence which in many circuits is potentially very powerful can produce a drastic restriction of flow upon increased sympathetic discharge. Here it should be remembered however that the supply of constrictor nerves seems to be more pronounced the less vitally important and the less sensitive to ischemia the respective tissues are. Therefore in states of a failing cardiac output for example an intensified constrictor fiber discharge will direct the blood flow in the first place to the central nervous system and the myocardium; this is a kind of centrally governed rationing of supply in time of need.

In contrast to these principles governing the control of the *flow resistance* wherein a myogenic activity appears to be a fairly dominating feature the situation on the venous side is strikingly different.[10] In all probability there is some myogenic activity present here as well but it is largely confined to the venules only.[illegible] Thus when considered in terms of its capacitance function venous control is not dependent on such a locally originating mechanism but appears to be almost entirely dominated by its extrinsic nervous supply.[10] As will be further discussed below the vasoconstrictor fiber control on the venous side is so dominating that it is able to overrule other types of influences such as local vasodilator factors to a considerably greater extent than that which is possible with regard to the precapillary resistance vessels.

One may ask why the veins show such a contrast to the precapillary resistance vessel in the matter of the balance between local and nervous mechanisms. It may be recalled that another functionally specialized vascular section—the arteriovenous anastomoses of the skin—is characterized by an almost complete lack of inherent smooth muscle activity but is instead directed by a powerful and dominating vasoconstrictor fiber influence.[illegible,17] It appears as though the vascular smooth muscles of this specialized section as well as those of the venous capacitance section have become differentiated in a direction similar in the organization of their control to that of the intrinsic smooth muscles of the eye or more extremely so the skeletal muscles. A shift from a mainly local effector control to a centralized one is the natural development of course whenever a particular function has to be centrally integrated to subserve the organism in the best way. This is the case with both venous capacitance function and the function of the cutaneous arteriovenous shunts. The veins here subserve the integrated cardiovascular performance as an adjustable forechamber for maintaining the pump output at an adequate level and the arteriovenous shunts subserve the centrally integrated regulation of temperature of the organism.

Another difference between the capacitance and the resistance vessels of any given vascular circuit is revealed when they are both exposed to a gradually increased vasoconstrictor fiber activity. If the stimulation frequency is plotted along the abscissa for a stepwise increase in the rate of constrictor fiber excitation and the effector response is plotted in percentage of the maximal effect along the ordinate it is found that this frequency response curve for the capacitance vessels is quite clearly placed to the left of that for the resistance vessels. In other words the curve rises more steeply at lower frequencies but levels off at a lower frequency range than does that for the resistance vessels. This implies that even if the gradual reflex increase in sympathetic discharge is entirely uniform in rate, e.g., in response to bleeding, the constriction of the capacitance side of the vascular bed will tend to precede that of the resistance side. Such an adjustment compensates of course more adequately for a loss of blood than does a primary restriction of the blood supply. The flow resistance will increase more strikingly first when additional bleeding causes more intense sympathetic discharge and the neurogenic capacitance depot mobilization begins to reach its limits. Such a difference in the responses of the capacitance and resistance neuroeffectors may be simply and adequately explained by the difference in the wall to lumen ratio between arterial and venous vessels.

In general with an increase in neurogenic resistance another important phenomenon

follows, viz., a progressive increase in the precapillary to postcapillary resistance ratio and a consequently intensified mobilization of interstitial fluid to the circulatory system. It is interesting to note in this connection that some recent studies in this department indicate that the most sensitive baroreceptor-determined modulation of flow resistance in the major systemic vascular circuits appears to take place within the skeletal muscle area, at least in cats.[1, 19] In combination with such reflex shifts in muscle blood flow resistance, especially pronounced shifts seem to occur in the precapillary to postcapillary resistance ratio. This causes relatively large variations in the mean hydrostatic capillary pressure in the skeletal muscles and thus in a filtration transfer in this particular tissue.[19] It might be emphasized that the skeletal muscles form one of the few tissues in the body which is substantial enough to allow for any more considerable drainage of interstitial fluid into the circulation and has, conversely, a high capacity for lodging the fluid during outward filtration from the vascular compartment. In the splanchnic area, on the other hand, the precapillary to postcapillary resistance ratio generally does not seem to be more significantly altered in connection with more prolonged neurogenic changes in resistance. Therefore, neurogenic adjustments of the vessels of this area, which in other respects is most important hemodynamically, appear to affect its filtration equilibrium only insignificantly under normal circumstances.[19]

The results of the above-mentioned study[19] may suggest that the relatively preferential reflex constrictor fiber adjustment of the precapillary to postcapillary resistance ratio taking place in the skeletal muscles is not primarily designed for maintaining *total* flow resistance at a given level—as it here contributes relatively little except during more intense sympathetic activity. It seems to be rather more important as a reflexly directed regulator of the distribution of fluid between the intravascular and extravascular compartments of the extracellular space, i.e., helping to maintain the plasma volume constant. Here, again, the veins in their role of postcapillary resistance vessels seem to participate in a centrally directed homeostatic mechanism.

There is evidence to indicate also that the "hormonal link" of the sympatho-adrenal system usually has an effect on the *venous* system similar to that of the constrictor nerves. Epinephrine, which in low concentrations is a potent dilator of the resistance vessels in skeletal muscle, thus appears to exert a pure constrictor action on the corresponding capacitance vessels. In general, however, the constrictor effects of "physiologic" amounts of the catecholamines, whether released by activation of the sympathetic-adrenal medullary nerves or infused into the blood stream, are far weaker in extent than those exerted by the direct vasoconstrictor fiber innervation.[illegible] In this connection, it might be interesting to note that some pharmacologic agents seem to produce different response patterns in the resistance and in the capacitance vessels of the same tissue. Thus, whereas acetylcholine[3, 8] and isopropyl noradrenaline[illegible] are potent dilators of both these sections, histamine[3] and hydralazine[20] almost exclusively dilate the resistance vessels and nitrites,[8] on the other hand, have their main dilator action on the capacitance vessels. Again, angiotensin has been found to exert a much more pronounced constrictor effect on precapillary than on postcapillary vessels.[22]

The dual control of the peripheral vascular bed exercised by locally produced metabolic factors, on the one hand, and by the centrally governed sympathetic constrictor fiber system, on the other, implies that in many situations the "tone" of the vascular smooth muscles will depend on a competition between these two opposing forces. For instance, it has been shown that in skeletal muscle the precapillary vessels (precapillary resistance vessels and especially the sphincter vessels) are more sensitive to the dilator metabolites than are the postcapillary vessels (postcapillary resistance vessels and main capacitance vessels) when both are simultaneously exposed to a constrictor fiber influence.[21] The functional significance of such an organization is not immediately obvious in the resting equilibrium. It will become definitely apparent, however, in situations in which there is concomitantly

an extreme accumulation of vasodilator metabolites and a pronounced increase in the constrictor nerve fiber discharge. Such situations are met with, for instance, in hemorrhagic shock with a reduced supply of blood to the tissues or during exercise with increased muscle metabolism.[78] This general tendency of the metabolites to overrule the neurogenic tone in the precapillary section helps to maintain a nutritional flow of blood relative to the prevailing local metabolic demands. It further tends to distribute the available blood stream over a greater capillary surface area, which allows a more uniform capillary exchange within the tissue. The relative dominance of the centrally directed constrictor fiber influence on the capacitance vessels, on the other hand, will in such situations prevent peripheral pooling of blood and help to ensure the maintenance of an adequate venous return by mobilization of blood from the constricting veins.

In most cases of such an accumulation of vasodilator metabolites the normal ability of the constrictor nerves to maintain or even to increase the precapillary to postcapillary resistance ratio can largely be upheld, thereby allowing for an absorption of extravascular fluid if the constrictor fiber activity is intense enough. It is only in extensive muscular work or under exceptional circumstances, for example, late in the course of hemorrhagic hypotension, that a shift toward an outward filtration can occur. The precapillary resistance response to sympathetic activation then becomes almost abolished, whereas the postcapillary resistance response, i.e., that of the veins, is somewhat better maintained. This will lead to a *decrease* in the precapillary to postcapillary resistance ratio, a consequent net rise in capillary pressure and hence an outward filtration.[14] It is noticeable that at such an advanced stage of shock the sympathetic nerves are no longer able to act in their normal compensatory manner for combating the circulatory insufficiency but may, in fact, help to produce a progressive derangement because of such a continuous transcapillary loss of fluid from the circulation. Again, the functional characteristics of the veins and their specialized control are of great importance in this complex integration.

As mentioned above, the great distensibility of the veins may in some situations be disadvantageous to the cardiovascular system, for example, in the erect position unique to man and some primates. The major circulatory changes which occur when a shift is made from the supine or four-limb position to the erect position are connected with the great hydrostatic load that is suddenly exerted on the capillaries and the large fraction of the distensible venous side that is then situated below the level of the heart. Several counteracting mechanisms are, however, brought into play to decrease the tendency of transcapillary loss of fluid and venous pooling of blood. In the abdomen, the hydrostatic tissue pressure of the soft internal organs is likely to be closely similar to that produced if the abdomen were filled with fluid. This creates an extramural pressure that almost exactly balances the raised intravascular pressure. In the extremities, venous pooling is, of course, to some extent similarly prevented in this case by the external support exerted by rigid enclosing structures, such as skeletal muscle fasciae, etc. Moreover, valves which are here situated at strategic points in the veins not only prevent backflow but may also interrupt the continuous column of blood, at least intermittently. With continuous venous flow, on the other hand, the valves are open and then the hydrostatic load of a continuous column of blood is transmitted to the lowest parts of the circulatory system. An important countermeasure here is the pumping action of contracting skeletal muscles, which will temporarily diminish the hydrostatic increment of venous and mean capillary pressures and thereby help to counteract pooling of blood and outward filtration. Also of utmost importance during postural changes is the action of the vasomotor nerves, which mediate reflex constriction of the capacitance vessels in the erect position, opposing the distending forces in the dependent regions. Moreover, the reflex activation of the vasoconstrictor nerves accomplishes a certain mobilization of reservoir blood from other less dependent regions, both in the lesser and the systemic

circulation, so that central venous pressure and venous return are not interfered with too much. The importance of the vasomotor control of the capacitance vessels in this connection is readily understood from the pronounced orthostatic symptoms seen in subjects deprived of their sympathetic innervation by surgical or pharmacologic methods.

Protection against too serious a rise in capillary pressure in dependent regions during erect posture is also accomplished on the precapillary side. For instance, the precapillary to postcapillary resistance ratio will become increased partly because of the action of the sympathetic nerves and partly because of probable intensification of the myogenic automaticity of the precapillary resistance vessels. Such a facilitation of their myogenic activity may be expected to occur wherever their transmural pressure is raised in dependent vascular areas.[illegible] Even more important in this connection is the effect of the reinforcement of the myogenic automaticity on the precapillary sphincters which occurs when transmural pressure is raised. This leads to closure of a number of sphincters so that blood flow is shunted through fewer capillaries than normally. With this the capillary surface area available for flow and hence for filtration exchange is reduced. The functional capillary surface area in the human foot has been shown to decrease to one third to one eighth of normal on shift of the body to erect posture and the tendency for filtration loss of fluid correspondingly decreased.[illegible] This is probably one of the most important mechanisms which protects against the formation of edema in dependent regions.

Mention has been made of some circulatory adjustments, e.g., during hemorrhage and during postural changes, etc., when a reflex increase in the sympathetic vasoconstrictor fiber discharge occurs. Thus it seems to be well established that both the aortic and carotid baroreceptors and also the chemoreceptors participate in the regulation of both the resistance and the capacitance vessels.[illegible] Changes in the baroreceptor activity during arterial hypertension and hypotension will thus help to adjust the venous blood capacity in relation to the demands for maintaining an adequate venous return. Whether the influence of this reflex control is entirely uniform with respect to the constrictor fiber discharge to the resistance and the capacitance side of the circulation is so far not known for certain;[illegible] some data may suggest that this is not necessarily the case, but it is at present premature to give any definite statements. It has already been outlined how the precapillary and postcapillary resistance vessels are reflexly affected to a different extent in various tissues.[illegible] However, these differences are not necessarily a consequence of distinct differentiations in constrictor fiber discharge. They may well be a matter of quantitative regional differences in the effector sensitivity to the opposing effects of the constrictor mediator and local vasodilator influences.

Reflexes elicited from the low pressure regions of the circulation might well deserve special attention with regard to the regulation of venous tone. It has been demonstrated that activation of central venous, cardiac, and pulmonary receptors may lead to bradycardia, arterial hypotension, and venodilatation.[illegible] We have, however, still no clear evidence as to the quantitative influence of such reflexes on the precapillary and postcapillary side of the circulation. At first sight it might seem to be an attractive hypothesis that such low pressure receptors, particularly those activated by distention of the central veins and the atria of the heart, might be more preferentially engaged in the control of the veins. As strategically well placed receptors they would then be able to adjust central venous pressure and also prevent overloading of the heart by relaxing the venous side of the vascular bed when necessary. However, if such a hypothetical preferential reflex engaged the entire venous side, this would also include the postcapillary resistance vessels. Then it would at the same time tend to increase the precapillary to postcapillary resistance ratio. This would in turn increase the intravascular fluid volume by causing an inward filtration, but this would hardly be rational in the situation. Obviously, hypotheses in this complex field run the risk of being invoked too early, and more experimental work is badly needed before more

definite statements can be made. It is unfortunate that an adequate and at the same time selective stimulation of these low pressure receptors often seems to involve serious interference with normal cardiac performance. It is also very difficult to avoid a secondary interference with the arterial receptor mechanisms. Therefore hitherto available results of such experiments can hardly be interpreted in quantitative terms with respect to the reflex effects on total flow resistance, precapillary to postcapillary resistance ratio, and capacitance function. Much more could be said about these complex and interesting questions but it would lead us too far away from the point. It is also beyond the scope of the present survey to discuss the interesting finding that cardiac receptors may control the fluid volume of the organism via different renal mechanisms. This problem is discussed in detail by Gauer, Henry, and Sieker.[44]

Beside these examples of visceromotor reflexes elicited from receptors situated within the cardiovascular system, venous adjustments seem to occur in connection with reflexes emanating from sites outside the circulation. Thus it has been established that Group III muscle afferents, which probably convey deep pain, produce at the bulbar level a reflex inhibition of the tonic sympathetic discharge together with a vagal activation. This reflex response leads to bradycardia and to pronounced arterial hypotension which is caused largely by a dilatation of both the resistance and the capacitance vessels. A similar reflex pattern may also be elicited from what is thought to be similar afferent fibers emanating from visceral organs in the abdomen. It has been suggested that such dramatic changes in cardiovascular dynamics, which thus also engage the venous side, may be responsible for initiating the type of syncope that sometimes occurs in connection with blunt trauma to skeletal muscle or internal organs. Excitation of pain fibers from the skin generally has the opposite effect, namely, an increase in the sympathetic discharge, which in all probability also affects the venous side of the circulation. There is evidence to indicate that the venous system is engaged in many other reflex patterns, for example on exposure to cold and exercise[17] or to hyperventilation and mental excitation. It seems reasonable to conclude that most stimuli which by the vasomotor pathways affect the resistance side of the circulation will concomitantly influence the venous system in a similar direction, but possibly not always to the same extent.

It is evident from what has been said that the vasomotor center in the oblongata medulla, by its spontaneous tonic discharge steadily modified by the cardiovascular receptors and sometimes also by other receptors, will be a major determinant of venous tone. As also mentioned, the nervous control may, relatively speaking, be even more dominating on the capacitance vessels than on the resistance vessels, partly because of the fact that their curve of frequency response to sympathetic activation has a different shape and partly because the veins exhibit far less inherent myogenic activity and are relatively less affected by opposing chemical factors. It may then be questioned whether, beside such a differentiation at the neuroeffector level, special structures might also exist at higher levels of the central nervous system which preferentially, or even exclusively, affect the venous compartment to ensure immediate mobilization of the peripheral depots. As yet it has not been possible to detect any functionally separate "venomotor center," and the vasomotor fibers normally seem to be engaged in certain patterns rather than working selectively.

Evidence is now accumulating to show that highly differentiated patterns of response with regard to reactions of the resistance and capacitance vessels can sometimes be elicited from centers above the brain stem. To exemplify, it is known that topical stimulation in the hypothalamic sympathetic vasodilator area produces a pronounced dilatation of the resistance vessels of the skeletal muscles by way of sympathetic cholinergic vasodilator fibers distributed only to this tissue. The muscle capacitance vessels are, however, not dilated; on the contrary, such stimulations generally produce a definite constriction of the muscle capacitance vessels[41] and also produce tachycardia and constriction of both the resist-

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The effect of digitalis upon the exercise electrocardiogram

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The electrocardiographic exercise test is being used with increasing frequency as a means of detecting coronary artery disease and in evaluating work capacity in patients with known cardiac lesions. Occasionally, the test is employed in patients who are receiving digitalis preparations. Several workers have pointed out that under these circumstances diagnostic S-T segment depression during exercise may occur in subjects who are free of coronary disease.[1-4] However, one study demonstrated that in 15 patients with angina and a positive ECG exercise test, only one developed a more positive test after the administration of digitalis.[4] Few systematic controlled studies of this problem have been carried out. The following study was undertaken to evaluate the effect of digitalis upon the ECG exercise test in normal subjects and in patients with heart disease. In addition, various mechanisms by which digitalis preparations may affect the exercise test have been examined.

Material and methods

Thirty-one subjects were studied. Fifteen had known or suspected cardiac disease, whereas 16 were normal students or house officers (Table I). The ECG exercise test always consisted of a double two-step test (Master's test) performed under uniform conditions. After the initial test had been performed, digoxin (Lanoxin) was given orally in a dose of 1.5 to 2.0 mg. the first day, 0.5 to 1.0 mg. the second day, and 0.25 to 0.50 mg. on the third and in some instances also the fourth day. The total amount given in 3 days varied from 2.5 to 4.0 mg. The ECG exercise test was then repeated in exactly the same manner. After a 30 minute rest period, during which the electrocardiogram had returned to its resting level, an additional exercise test was carried out in selected subjects under the following conditions: (1) During inhalation of 100 per cent oxygen provided by means of a mouthpiece connected to a low resistance demand valve. A nose clip was used and the rise in arterial oxygen saturation to 100 per cent was confirmed by an earpiece oximeter. (2) Two minutes after a nitroglycerin tablet (0.40 mg.) had been placed under the tongue. (3) After the administration of a potassium solution (Potassium Triplex). Three subjects received 60 mEq. of potassium over a period of 24 hours prior to exercise, and 2 subjects received from 90 to 150 mEq. in 3 hours

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Table I. Clinical material and results of experiments

	Subject	Diagnosis	Age	Sex	Exercise test without digitalis	Exercise test with digitalis
1	R G	Mitral insufficiency	20	M	+	++
2	L D	Myocardial infarction, old	61	M	+	++
3	A F	Aortic valvular stenosis	25	M	+	++
4	P R	Chest pain of unknown origin	45	F	±	+
5	J C	Atrial septal defect, postoperatively	36	F	±	+
6	N C	Myocardial infarction, old	41	M	−	−
7	G M	Polycythemia vera	25	M	−	+
8	M D	Possible coronary insufficiency + paroxysmal tachycardia	41	F	±	+
9	J B	Chest pain of unknown origin	27	F	±	+
10	R L	Essential hypertension	39	F	−	+
11	F F	Angina pectoris	33	M	+	++
12	H H	Myocardial infarction, old	49	M	−	+
13	A B	Essential hypertension	44	M	+	++
14	B B	Angina pectoris	47	F	+	++
15	G H	Chest pain of unknown origin	48	F	−	+
16	C K	Normal	34	M	−	+
17	H M	Normal	26	M	−	−
18	J R	Normal	26	M	−	−
19	A S	Normal	23	M	−	+
20	W F	Normal	32	M	−	+
21	S L	Normal	23	M	−	+
22	L T	Normal	22	M	−	+
23	S T	Normal	22	F	−	+
24	J L	Normal	23	M	−	+
25	L W	Normal	22	M	−	−
26	E P	Normal	23	M	−	−
27	H K	Normal	27	M	−	+
28	R M	Normal	26	M	−	−
29	Y M	Normal	24	F	−	−
30	J L	Normal	20	M	−	+
31	E K	Normal	23	M	−	+

Key: 0, Not done; −, No effect on ECG; ±, Borderline effect on ECG; +, Definite effect on ECG; ++, Marked effect on ECG.

to 45 minutes before exercise. However, in almost all instances the last dose of potassium was given approximately 90 minutes prior to the exercise test, at which time the electrocardiographic evidence of potassium effect reaches its maximum.[13]

In some normal subjects the effect upon the electrocardiogram of breathing a mixture low in oxygen (10 or 8 per cent oxygen in nitrogen) as long as tolerated up to 20 minutes was examined before and after the administration of digoxin. Samples of venous blood were drawn in selected subjects before and immediately after exercise. Concentrations of sodium and potassium in the serum were determined by flame photometry and hematocrits were measured by the Wintrobe technique. Three weeks after digoxin was discontinued, final exercise tests were performed in all subjects to eliminate temporal effects upon the test. In some patients who had already been on digitalis preparations, the initial exercise test was done during digitalization. The second exercise test was performed at least 1 month after cessation of digitalis administration. All electrocardiograms were recorded at standard paper speed using a Sanborn direct writing instrument.

The following criteria proposed by Master[7] were used to identify a positive exercise test: (1) any S-T depression of 2.0 mm or more, (2) a J depression of rela

Total dose of Lanoxin (mg)	Number of days	100 per cent oxygen	Low oxygen: No digitalis	Low oxygen: Digitalis	Nitroglycerin tablet (increased S T segment depression)	Administration of K (decrease or elimination of S T segmental depression)
2.75	3	0	0	0	0	0
2.50	2	0	0	0	0	0
3.25	4	0	0	0	0	0
2.50	3	0	0	0	0	0
1.50	3	0	0	0	0	0
2.75	3	0	0	0	0	0
2.50	2	0	0	0	0	0
Gitaligen	2–3 mo	0	0	0	0	0
Dig folia	1 mo	0	0	0	0	0
2.75	4	0	0	0	0	0
4.00	4	0	0	0	0	0
4.00	4	0	0	0	+	0
4.00	4	0	0	0	0	0
4.00	3	0	0	0	0	0
Digitoxin	1 mo	0	0	0	+	
3.5	3	+	–	0	+	0
3.5	3	–	0	0	0	0
3.5	1	0	0	0	0	0
3.5	1	+	–	0	0	0
3.75	3	+	0	0	0	0
4.0	4	+	–	0	0	+
3.5	4	+	–	0	0	0
4.0	4	±	–	0	±	–
4.0	4	+	–8C	–	0	–
3.5	3	0	0	0	0	0
4.0	1	0	0	0	0	0
4.0	4	+	–8C	+8C	0	+
3.5	3	0	–8	+8C	0	0
3.5	3	0	–	±	0	0
3.5	3	+	0	0	–	0
4.0	4	±	0	0	0	+

Low oxygen refers to 10 per cent oxygen [illegible]

tively long duration, a $\frac{QX}{QT}$ fraction of 50 per cent or more or a Q T ratio of 1.08 or more or both (3) ischemic S T depressions completely horizontal or with sag.

Results

Subjects with cardiac disease All patients had sinus rhythm at rest and during exercise with or without digoxin. Only rare extrasystoles occurred during exercise. Chest pain did not occur during the exercise tests.

In 4 of 15 patients a negative exercise test became clearly positive after digoxin and became negative again when digoxin was discontinued. An example is shown in Fig 1. A 48 year old woman had experienced episodic chest discomfort of unknown cause for 6 years. She had been given a trial of digitoxin for 2 months (dose of 0.1 mg daily). During this time a positive exercise test was recorded (*A*). Three months after cessation of digitoxin the exercise test was negative (*B*). The chest discomfort remained unchanged.

In 10 of 15 patients a borderline or positive exercise test became clearly positive or more positive after the administration of digoxin. A 25 year old man with valvular aortic stenosis and mild effort angina had a clearly positive initial exercise test. The depressed S T segment re

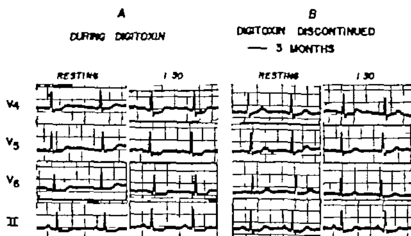


Fig. *1* G H a 48-year old woman with chest pain of unknown origin. *A* During administration of digitoxin. Resting ECG demonstrates sagging of the S-T segment in Lead V and II but the S-T segment in Lead V_4 is at the isoelectric level. Immediately after exercise so-called ischemic S-T segment depression of approximately 1 mm is seen in Leads V and II. *B* Three months after cessation of administration of digitoxin. Normal resting ECG and negative exercise test.

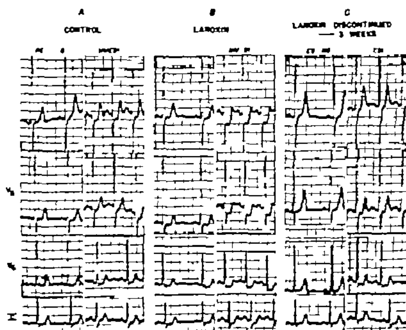


Fig. \ F a 25 year-old man with arterial hypertension. *A* Control (before administration of digoxin). Positive exercise test showing 3 mm depression of the S-T segment in Lead V immediately after exercise. *B* During administration of digoxin. Resting electrocardiograms are similar to previous control record. Note marked ischemic S-T segment depression in Lead V immediately after exercise. *C* Three weeks after cessation of digoxin. Resting and exercise electrocardiograms are similar to those of control except for slight increase in T wave voltage in Leads V.

turned to the pre-exercise level 2 minutes after exercise After digoxin the same amount of exercise produced more striking S T segment depression which lasted for more than 2 minutes after exercise Three weeks after the cessation of digoxin the test ECG resembled the initial record (Fig 2)

Only one patient (Case 6) with a slight depression of the j point prior to digoxin failed to develop a clearly positive test during the administration of digoxin Depression of the j point became slightly greater but was not sufficiently so to satisfy the previously described criteria

Normal subjects Prior to the administration of digoxin all exercise electrocardiograms in this group were negative The administration of digoxin was accompanied by the appearance of a positive exercise test in 10 of 16 subjects (61 per cent) Eight of these subjects had ischemic S T segment depressions of at least 1 mm Two had junctional depressions of 1 mm with a

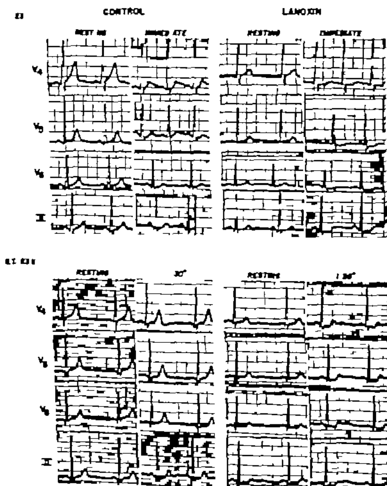


Fig 3 *Upp* \ S a 73 year-old healthy man Control (before admin tration of digoxin) Normal resting ECG and negative exercise test During admini tration of d goxin the T w es are lowered in the resting record Im mediatel after exercise ischemic S-T segment depression is seen in Lead \ and II *Low* S T a 73 year-old healthy woman Control (before ad ministrati of d goxin) Normal rest ng ECG and negati e exercise test During administration of d gox n there is a sagging of the S-T segment and lower ing of the T w es in Lead \ and II in the re ting record One and one half minutes after exercise the ischem S-T segment depression of t lea t 1 mm is shown in Leads \ and II

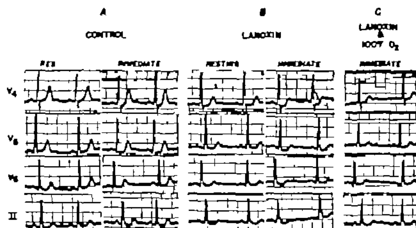


Fig. 4. S. L., a 23-year-old man. A, Control (exercise breathing room air before digoxin). Normal resting record and negative exercise test. B, During administration of digoxin. Lowering of the T wave and slight sagging of the S-T segment are seen in the resting record. Ischemic S-T segment depression in Lead V_4 immediately after exercise during breathing of room air satisfies the criteria for a positive exercise test. C, Immediately after exercise breathing 100 per cent oxygen. No definite ischemic S-T segment depression is present. The heart rate is slightly slower. Negative exercise test.

$\frac{QX}{QT}$ ratio exceeding 50 per cent. In some subjects whose exercise tests remained negative, 0.5 mg. of digoxin was given for an additional day without an effect upon the test. One subject developed a transient coronary sinus rhythm after exercise both before and during the administration of digoxin, but a positive exercise test did not appear. Two examples of the occurrence of positive exercise tests during the administration of digoxin are illustrated in Fig. 3.

Effect of breathing oxygen. Ten normal subjects who developed positive exercise tests during the administration of digoxin were exercised while they breathed 100 per cent oxygen. In each instance the S-T segment depression induced by exercise was decreased or eliminated by the breathing of oxygen. An example is shown in Figs. 4 and 7. The heart rate during exercise tended to be slightly lower during the administration of oxygen.

Effect of acute hypoxia. Seven normal subjects who had developed positive exercise tests while receiving digoxin were subjected at a later date to acute hypoxia. Digoxin had been discontinued for at least 3 weeks. None developed a positive test despite rather severe hypoxia which often produced dyspnea, dizziness, throbbing sensations in the head, and cyanosis.

Hypoxia studies were then performed on 4 normal subjects while digoxin was being given. Three subjects developed S-T segment depressions which were marked in 2 who received 8 per cent oxygen and slight in 1 who received 10 per cent oxygen. The test was repeated after digoxin had been discontinued, and no S-T segment change was produced (Fig. 5).

Effect of nitroglycerin. Two patients and 3 normal subjects whose initial negative test became positive with digitalization were studied while still taking digoxin. The administration of nitroglycerin did not modify the positive exercise test, and in all but one subject the S-T depression during exercise became somewhat greater (Fig. 6). In the 2 patients the heart rate during exercise was slightly greater after nitroglycerin. This was not observed in the 3 normal subjects.

Effect of potassium. Five normal subjects whose exercise test had become positive while receiving digoxin were selected. Potassium Triplex (60 mEq. in 24 hours) did not affect the exercise test in 2 subjects although increased amplitude of the T waves in the resting and exercise tracings

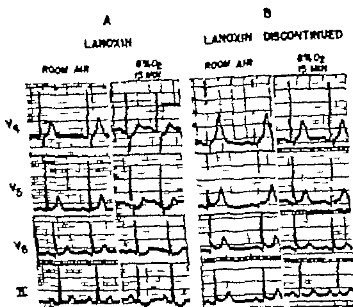


Fig. 5. H. K., a 77-year-old healthy man. A. During administration of digoxin. Normal ECG with breathing of room air. Fifteen minutes of breathing 8 per cent oxygen cause ischemic S-T segment depression in Leads [illegible] and T wave inversion in Lead II. B. Three weeks after cessation of administration of Lanoxin. Normal ECG with breathing of room air. The T waves are slightly higher than before. Fifteen minutes of breathing 8 per cent oxygen results in no S-T segment or T wave changes.

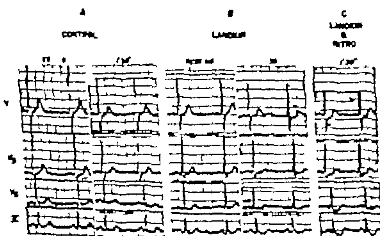


Fig. 6. A 49-year-old man with history of old myocardial infarction. A. Control. Normal resting ECG and negative exercise test. B. During administration of digoxin. Normal resting ECG. The T waves are slightly lower than those of control. One and one-half minutes after exercise, ischemic S-T segment depression (0.5 mm.) is seen in Lead V. Borderline positive exercise test. C. After administration of nitroglycerin. Ischemic S-T segment depression of [illegible] mm. has appeared in Lead V after exercise (1 minute and 30 seconds). Definite positive exercise test. The heart rate [illegible] slightly faster than before administration of nitroglycerin.

Table III. Statistical analysis of changes in serum electrolytes and hematocrit after exercise before and during digitalization in normal subjects

	Before digitalization			During digitalization		
	Pre-exercise	*Postexercise*	*Rate of increase (%)*	*Pre-exercise*	*Postexercise*	*Rate of increase (%)*
Serum K						
Mean	4.0 mEq./L. ⟶	4.4	+10	4.2 mEq./L. ⟶	4.6	+10
Number of case	16	16		16	16	
S.D.	0.32	0.4[illegible]		0.24	0.32	
Serum Na						
Mean	144 mEq./L.	146	+ 1	144 mEq./L.	145	+ 1
Number of case	16	16		16	16	
S.D.	2.7	3.6		[illegible].0	1.98	
Hematocrit						
Mean	44.9%	45.5	+ 1	45.1%	46.4	+ 3
Number of case	13	13		13	13	
S.D.	3.2	2.9		2.7	2.7	

*p < 0.01
†p < 0.001
S.D. Standard deviation.

positive exercise test in patients with coronary disease. A Q-T ratio* of 1.08 or greater (as calculated from Bazett's formula) is usually present in a positive test. In this study 4 patients had prolonged Q-T ratios which fulfilled the above-mentioned criterion after exercise. One had an old myocardial infarction, 1 had aortic stenosis, and 2 had possible coronary disease. The Q-T ratio was prolonged both before and after the administration of digoxin. None of the normal subjects, however, had Q-T ratios which exceeded 1.08 even when S-T segment depression occurred after exercise while they were receiving digoxin. Moreover, a widely accepted view that the action of digitalis reduces cardiac output and exerts an unfavorable influence upon the normal circulatory system[9,10] was denied by Selzer and associates[11] who showed that digitalis exerts no significant hemodynamic influence upon the circulation in the absence of cardiac disease or failure. In addition, it is a well-known clinical observation that anginal pain is not made worse by the administration of digitalis.

It seems unlikely, therefore, that digitalis alters the exercise electrocardiogram by the production of myocardial ischemia or myocardial anoxia.

The present study clearly indicates that potassium salts lessen or abolish the S-T segment depression that occurs during exercise in a digitalized subject. There is some evidence to suggest that the S-T segment depression produced by digitalis preparations in both the resting and postexercise ECG may be due to the loss of potassium from the myocardium. Ouabain has been shown to cause a loss of potassium from the rabbit atrium.[1] Helkins and co-workers[10] have demonstrated that acetylstrophanthidin administered to dogs caused a prompt rise in the concentration of potassium in the coronary sinus compatible with a loss of potassium from the myocardium. It has also been suggested that exercise may be accompanied by the loss of potassium from the myocardium.[1] In the present study the rise in serum potassium induced by exercise could be due

*Q-T ratio = Measured Q-T interval / Corrected Q-T interval

Corrected Q-T interval = 0.4 $\sqrt{RR}$ (Bazett's formula)

in part to loss of potassium from the myocardium although skeletal muscle may also be involved The administration of potassium salts may inhibit the loss of myocardial potassium during exercise in the digitalized subject and thereby prevent the S T segment depression This is also suggested by the fact that when patients were given potassium salts the expected rise in serum potassium did not occur after exercise Furthermore oxygen may exert an effect on the exercise ECG during digitalization by changing the permeability of the myocardial cell membrane to electrolytes If this is the case even the results of breathing oxygen in this study will support the present view

Several practical points can be derived from this study It is clear that approximately 60 per cent of normal subjects may develop positive ECG exercise tests as a result of the administration of digitalis With the exception of prolongation of the Q T ratio the ECG changes fulfill the accepted criteria of a positive test It seems unlikely that the ECG changes induced by exercise in the normal digitalized subject are due to myocardial ischemia and therefore so called ischemic S T segment depression in the exercise ECG may not always necessarily indicate myocardial ischemia However this does not reduce the importance of the ischemic S T segment depression in the exercise ECG for the detection of coronary artery disease in undigitalized patients which has been stressed repeatedly by many authors [11,17] The application of more rigid criteria for a positive test (1 mm ischemic depression of the S T segment of at least 0 08 second duration) will not entirely eliminate the falsely positive test that results from digitalization

In the interpretation of routine electrocardiograms it is often helpful to identify a positive exercise test in a digitalized subject Two clues may be useful If the initial tracing demonstrates a short Q T interval and a slight sagging of the S T segment one may suspect that digitalis is being given Any S-T segment depression induced by digitalis in the resting record usually will indicate that a positive test will occur on exercise The second clue is the failure of the Q T interval to become prolonged after exercise—A Q T ratio of 1 08 or greater suggests digitalis effect rather than coronary disease If a digitalis preparation is being given one should discontinue the drug and wait at least 3 weeks before repeating the test since even rapidly acting preparations such as digoxin may exert effects for a week and a minute amount of radioactive digitoxin can be detected for as long as 6 weeks [9] after discontinuance of the drug

Summary

1 Electrocardiographic exercise tests (Master s 2 step test) were performed in 15 patients and 16 normal subjects before and after full digitalizing doses of digoxin (Lanoxin)

2 While receiving digoxin 14 of 15 patients and 8 of 16 normal subjects developed positive tests Five of the 15 patients and all of the normal subjects had negative tests when not receiving digoxin

3 Although the mechanism of the effect of digoxin upon the ECG exercise test remains unknown no evidence was found to suggest that myocardial ischemia was produced by the drug An effect upon intramyocardial potassium seems to be most likely

4 ECG exercise tests should not be carried out in patients who are receiving digitalis preparations Digitalis should be discontinued for at least 3 weeks before an exercise test is performed

5 Examination of the Q T ratio may enable one to differentiate a false positive test due to digitalis from a true positive exercise test

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

Diuretic therapy
Part IV. Pharmacology of thiazide diuretics

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The introduction in 1957 of chlorothiazide, an oral diuretic of high potency and well tolerated by most patients, has been of great help to the clinician in the control of the retention of fluid. Many congeners designed to reduce the complications of chlorothiazide are now available. This group of drugs is commonly referred to as *thiazides*. The basic structure is a heterocyclic acid containing a benzothiadiazine radical which incorporates two nitrogen atoms and one sulfur atom in one of the unsaturated rings. The prototype drug chlorothiazide has a chlorine atom and a sulfamyl group substituted on the benzene ring.

All of the congeners available except chlorthalidone contain this benzothiadiazine nucleus with various substituents. Chlorthalidone contains a phthalimidine nucleus rather than the benzothiadiazine ring, and thus is not properly a thiazide. It does have a substituent sulfamyl group and chlorine atom. Since chlorthalidone has pharmacologic actions similar to those of the thiazides, it is usually grouped with them.

Mechanism of action. Chlorothiazide produces increased excretion predominantly of chloride, much like a mercurial, rather than an increased excretion of bicarbonate and resultant metabolic acidosis typical of carbonic anhydrase inhibitors. As with mercurials and carbonic anhydrase inhibitors, the effect cannot be explained by an increased renal blood flow or increased filtered load of sodium, so that decreased tubular reabsorption of sodium must be implicated. The exact mechanism of this decreased reabsorption is not known, but it is clearly not the same as that with organic mercurials because (1) the maximum loss of sodium that can be produced by mercurials is greater than that produced by thiazides in acute studies, (2) there is a definite additive effect in natriuresis of thiazides upon mercurials, and (3) the effect of thiazides, unlike that of mercurials, is not inhibited by hypochloremic alkalosis.

The tubular site of action of thiazide diuretics is also unknown. Thiazides are excreted in the proximal tubule much like para-amino hippurate, but this does not prove that this is their site of action. Indeed, this excretion can be blocked by probenecid with little effect on the natriuresis. There are divergent interpretations of the available stop-flow experiments: some authors favor predominant proximal, whereas others favor predominant distal tubular action.

Mechanism of loss of potassium. In addition to this major effect on sodium and

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chloride reabsorption, thiazides do produce measurable inhibition of carbonic anhydrase. Chlorothiazide causes a greater inhibition of carbonic anhydrase than do other commonly used thiazides. Thus after acute administration of chlorothiazide there is a significant loss of bicarbonate and a greater loss of potassium than with the other thiazides. This effect, of course, would lead to a hypokalemic acidosis and has no relation to the clinically important hypokalemic alkalosis seen with chronic therapy, which is not due to carbonic anhydrase inhibition. This difference in carbonic anhydrase inhibition led to early claims of less loss of potassium for the newer congeners.

The wastage of potassium that frequently complicates chronic thiazide therapy occurs with all thiazide diuretics. Although some of this may be due to interference with the reabsorption of filtered potassium, the major cause is the increased load of filtered sodium which reaches the more distal sites of the sodium-potassium exchange mechanism. In response to this greater tubular load of sodium, the rate of tubular secretion of potassium and exchange with sodium is augmented, and an increased amount of potassium is lost in the urine. This rejection is determined by stimulation of mineralocorticoids, especially aldosterone, and bears no relationship to the chemical constitution of any particular thiazide. The sodium-potassium exchange mechanism is very sensitive to the level of aldosterone, and thus stimuli such as prior depletion of sodium, which increase aldosterone secretion, greatly increase the loss of potassium. Further evidence for this mechanism is the reduction in the loss of potassium produced by adrenalectomy or the use of aldosterone antagonists. Therefore, the degree of loss of potassium by a patient on chronic thiazide therapy is a result of the physiologic state of the patient rather than the particular diuretic.

In general, the loss of potassium with thiazide therapy is greater than with mercurials because (1) thiazides must often be given continuously, so that there is no opportunity for restoration of lost potassium between treatments, and (2) thiazides do not have an effect such as that of the mercurials in partially inhibiting the secretion of potassium.

Mechanism of unresponsiveness. Failure of diuresis may be due to one or both of two reasons. The first is a reduction in renal blood flow and glomerular filtration rate so that the tubular load of sodium is small and can be reabsorbed despite the diuretic. The second is a highly active sodium exchange mechanism which is able completely to substitute potassium (and ammonium) for sodium in the urine despite the effect of the diuretic in presenting more sodium to the more distal portion of the tubule. The second mechanism can be reversed by the addition of an aldosterone antagonist.

Mechanism of other actions.

1. EFFECT OF THIAZIDES IN INCREASING SPECIFIC GRAVITY AND REDUCING VOLUME OF URINE IN DIABETES INSIPIDUS. The increase in specific gravity can be readily explained when one recalls that dilute urine is produced by the reabsorption of solute *in the distal tubule* because of the impermeability of the distal tubule to water in the absence of antidiuretic hormone. If the reabsorption of sodium is blocked by thiazides, then distal tubular dilution will not occur to the same degree and the urine will contain more solute and have a higher specific gravity.

The reduction in the volume of urine which has been reported to be as much as 50 per cent, is not so easily explained. One explanation that has been offered is that the chronic depletion of sodium produced by thiazides causes a subtle change in serum osmolarity which reduces thirst and consequently the volume of urine.

In any case, thiazides are not so specific or effective as vasopressin in diabetes insipidus and should be reserved for cases that are resistant to vasopressin.

2. DIRECT HYPOTENSIVE EFFECT IN THE PRESENCE OF HYPERTENSION, ESPECIALLY THAT OF POTENTIATING THE EFFECT OF OTHER HYPOTENSIVE DRUGS. Early in the course of thiazide therapy in a hypertensive patient there is a fall in blood volume and cardiac output and an increase in calculated peripheral resistance in association with the fall in blood pressure. These findings suggest that the fall in blood pressure is due to sodium depletion; this

is further supported by a similar hypotensive effect of other diuretics and by the hypotensive effect of severe sodium restriction. However, after a few weeks reduction in cardiac output and blood volume can no longer be demonstrated by the methods available. It has been suggested by some that the persistent hypotensive effect can be explained by a fall in cardiac output within the margin of error of the technique. The demonstration that calculated peripheral vascular resistance may be reduced at this point suggests rather that thiazides have a direct vascular effect. On the basis of experiments in which the late hypotensive effect of thiazides was reversed by the ingestion of large amount of sodium chloride, it has been hypothesized that this presumed direct vascular effect is also due to sodium depletion, possibly because of a reduction in arteriolar thickness by a reduction in arterial cellular sodium. Differently designed studies have not confirmed the dependence of the hypotensive effect on sodium depletion, so that an entirely independent hypotensive effect of thiazides may exist.

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Annotations

Circulation in muscle during acute pressor responses to emotional stress and during chronic sustained elevation of blood pressure

During transient rises in blood pressure produced by an acute emotional stress such as asking the subject to carry out simple mental arithmetic at a speed with which he is unable to cope or frightening him about his state of health, blood is shifted from the kidneys, splanchnic region and skin to *the skeletal muscle where a marked vasodilatation* takes place. Because of these opposite changes in vascular tone the total peripheral vascular resistance may fall, remain unchanged or increase depending on the balance of vasoconstriction and vasodilatation in the various regions of the body. An increase in cardiac output is an integral part of this hemodynamic reaction. Only in those instances in which there is severe visceral vasoconstriction unbalanced by an equal increase in muscular vasodilation does total peripheral vascular resistance rise markedly and cardiac output remain unchanged or decrease, probably on the basis of reflex connections which exist between the peripheral vascular bed and the heart. A similar hemodynamic change accompanied by a rise in blood pressure has been produced in anesthetized cats and dogs by Eliasson and associates, who electrically stimulated *a zone* extending from the anterior margin of the supraoptic region posteriorly throughout the hypothalamus to *the level of the mammillary bodies. Abrahams and* Hilton demonstrated the same result in unanesthetized cats with electrodes implanted into the same hypothalamic region: stimulated by a current of low intensity these animals exhibited a behavior pattern reminiscent of the orientation or "what is it" reaction of Pavlov. With a current of higher intensity a typical rage reaction was produced. A similar regional hemodynamic effect can also be elicited by faradic stimulation of the motor cortex.[illegible] Although the visceral vasoconstriction is mediated by adrenergic sympathetic nerves, Folkow and Uvnäs have established that the vasodilatation in muscles during stimulation of the hypothalamus is potentiated by eserine and abolished by atropine and concluded that it is mediated by sympathetic cholinergic fibers.

Electrophysiologic exploration of the hypothalamus in human beings is of course difficult. However, the identity of the efferent pathways mediat*ing the emotional* hemodynamic response with those of the responses to hypothalamic stimulation favor an identity of mechanisms of the two reactions: the renal vasoconstriction produced by anxiety can be abolished by the administration of the adrenergic blocking agent Dibenamine.[illegible] Emotional vasodilation in muscle can be at least partly inhibited by stellate ganglion anesthesia and by *intravenous and especially intra-arterial atropine* injected into the vessel supplying the explored forearm muscles. This, along with an almost instantaneous onset of emotional vasodilation at least in some subjects, speaks in favor of a reflex nature and mediation by sympathetic cholinergic fibers. There seems to be, however, a humoral component involved also, judging from a delay period of as much as 35 seconds in some subjects and also from the incomplete blocking of the vasodilation by atropine, which completely abolished the action of a dose of acetylcholine chosen to produce a vasodilatation that was similar in magnitude to that previously brought on by emotional stress. This humoral agent, probably also active in animals in which section of the sympathetic nerve supply to the muscles does not entirely abolish the vaso*dilation produced by stimulation of the hypothalamus*, is still to be defined but might be epinephrine, which is liberated by hypothalamic stimulation, *the muscular vasodilatory effect of which is well* established.

Thus it appears that during emotional stress in human beings the hemodynamic reaction mobilized is the same as that in animals during faradic stimulation of their motor cortex and of a definite zone in the hypothalamus. Moreover, the hemodynamic response bears many analogies to that which accompanies strenuous muscular exercise.[illegible] That this hemodynamic change is also centrally mediated is suggested by the fact that it was possible to produce the same hemodynamic pattern by verbal suggestion of a strenuous muscular action.[illegible] It seems that the same type of hemodynamic response is elicited whenever the organism is faced with an unknown situation or stimulus which might be potentially dangerous. Under such conditions not only does the animal explore the stimulus with his sensory organs ("orientation reflex"), but the blood pressure transiently increases, blood flow in the skin drops and blood is apparently shifted to the muscular parts of the explored extremity

There are, however, some important differences. Whereas during emotional stress the increase in blood flow in muscle was found to occur simultaneously in all the regions studied, during muscular exercise this increase was limited only to the active regions. A finding to the contrary—an increase in blood flow in inactive muscle groups—has its explanation in the accompanying emotional factor and can be removed by previous training (Brod and Ulrych, unpublished data). Whereas in muscular exercise the enhanced supply of blood to the working muscles subserves their increased metabolic demand and is accompanied by an increased consumption of oxygen, increased arteriovenous oxygen difference, and increased consumption of glucose, this is not so during emotional hyperemia. Here the consumption of oxygen either changes not at all or increases very slightly, probably as a consequence of the increase in tone which can be demonstrated by electromyography. Glucose consumption also does not rise. The increase in blood flow is out of all proportion to the changes (if any) in oxygen consumption, so that the oxygen A-V difference invariably drops. Thus, during emotional stress the increase in blood flow in muscle occurs independently of any change in oxygen consumption and has obviously a different biologic basis. This is further corroborated by the fact that, whereas the extra blood during muscle exercise flows through muscle capillaries which have opened up at least partly under the influence of the accumulating vasoactive metabolites,[14] the extra blood during emotional hyperemia seems to flow through functional bypasses excluding the capillary blood bed. This is suggested by the absence of change in the slope of the disappearance curve of K injected into the muscle during the emotional stress, whereas there is a marked steepening of the slope during muscle exercise. Also, there is no change in the capillary filtration rate in the muscles during emotion, whereas muscle exercise is connected with an increase in this function (Prerovský, Ulrych, Heine, Linhart, Brod, unpublished data), which is obviously dependent in the first place on the size of the capillary surface, i.e., on the number of the patent capillaries.

Although the afferent side of the regulating mechanism effecting the shift of blood from the kidneys and splanchnic area during stressful exercise in man is not yet firmly established, it seems to be obvious that, with a given volume of blood, the opening of the vascular bed in the working muscles necessitates a closure of some parts of the vascular bed in other regions if the venous return and cardiac output are to be sustained (or even increased). That this response is coordinated at the cerebral level is suggested by the above-mentioned experimental work in which the same response could be elicited from the motor cortex. Mobilization of the same type of reaction during the rage reaction — with the foregoing is most readily understood in animal (cat). This action accompanies situations of acute threat to life which have to be faced by fight or flight, i.e., a violent muscular action on which the preservation of life depends. Also, situations connected with the orientation reaction might prove to be threatening and therefore necessitate the same muscular mobilization. If the greater fraction of the cardiac output is diverted to muscle, the animal will have an advantage should the situation prove to be dangerous and should immediate action be required, in contrast to a situation in which blood is pumped to muscle only when the maximum effort has already started. It is only with the development of civilized man that the environment has lost much of its threatening character; however, the threats to life have moved to a different plane and, although visible muscular action is suppressed by social inhibition, life situations which are accompanied by fear, anger, or anxiety still elicit the hemodynamic preparation for violent muscular action which accompanied such subjective feeling throughout thousands of years of phylogenesis.

This reaction, which prepares the circulation to an optimal efficiency should muscular action ensue, subsides as soon as the stimulus which produced this hemodynamic response is over. In some normotensive subjects these pressor responses, however, tend to be not only exaggerated but also protracted, and fair evidence exists that these subjects later develop permanent hypertension more frequently than do the normoreactors. Since the hemodynamic change underlying essential hypertension is analogous to that just described during acute pressor reactions, the conclusion seems justifiable that the permanent hypertensive state is due to some fixation of this preparatory hemodynamic pattern for muscular action. Whether this fixation is due to a wearing out of the central nervous system coordinating mechanisms of this response (in a way analogous to a steel spring which is eventually worn out by frequent use, this analogy applying even to the hereditary factor corresponding to the quality of steel) or to some other newly acquired pathology of coordinating mechanisms of the central nervous system or of the effector in the vascular wall has to be established by further research.

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Thoughts concerning spatial VCG systems*

The Committee on Electrocardiography and Vectorcardiography of the American Heart Association is entrusted with recommending a spatial vectorcardiographic system or systems for physicians to use in communicating their vectorcardiographic findings obtained from cardiac patients. Workers in the field appear to agree that the system( ) to be recommended should rest upon a sound biophysical foundation. At present several systems derived along this line exist with certain characteristics differe t ting one from the other.

Intermi t who have gained a thorough knowledge of and had sound experience in clinical cardiology, cardiac electrophysiology, and the biophysical foundation of vectorcardiographic systems under ta d that no present stem (nor any future ones) no matter how laborious ly d rived is clearly better than fellow systems of sound biophysical foundation, nor does any present system by its own merit deserve to be the spatial vectorcardiographic system for recommendation. Therefore members of the Committee a interm t with the aforesaid qualificat ns find it truly hard to recommend any system based upon the conventional criteria of selecti such as judges use to decide a contest. One fact that concerns all is that even in normal healthy man the electrical field on the thoracic wall usually assumes multipolar activity for a significantly long time during the ventricular depolarization.

An alternati e was to recommend several biophysically founded systems and let the individual physician select the one he preferred. It is true that among these systems there is a certain interchangeability th t usually is nonexistent among intuitive systems. But such interchangeabil ty is valid to a certain extent only with normal human subject. With cardiac patients, however, these biophysical lead systems are practically no not interchangeable in spite of a linear transformation. Obviously vector loops of different shapes recorded from several systems do not constitute a practical communicat ve solution.

After profound insight into these matters had been gained, there appeared to be no proper way to recommend any system. Yet there is definitely the need to communi te clinical vectorcardiographic finding in ter s identical description.

In true respect for our gre t teachers I w h to suggest systems utilizing the r famous contribu ti ns in vectorcardiography. Lamb owen laid the foundation of frontal plane vectorcardiography when in 1913 he introduced the equilateral tr

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angle for determination of the electrical axis In 1938 Wilson added a back electrode to form an equilateral tetrahedron and thereby initiated spatial vectorcardiography Burger in 1946 introduced (and completed in 1955) his equation for the scalene tetrahedron to provide spatial vectorcardiography with a biophysical foundation Therefore taken together the three limb electrodes the back electrode and the equations constitute the famous contribution in this field and are the components embodied in an electrical network which I formulated in a recent publication (Zao Z Z Valet ta Cardiovascolari 3:81 94 1962)

Supplementary to the routine 12 lead electrocardiogram the present network may be used to

M de special order by Sanborn Co Waltham M s

record vectorcardiograms and/or the N Y Z orthogonal lead Although vectorcardiographic findings thus a sume uniformity and become communicable to all physician concerned research in vectorcardiography encouraged for the purpose of clarifying certain basic i ues of importance for example the role of vectorcardiography in regard to congenital pediatric cardiacs or the effect of conductivity of various tissues normal and pathologic etc The new lead or system of lead resulting therefrom will serve only this said purpose

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Burlington Vt

Diurnal variation in plasma volume in normal and hypertensive subjects

Hypertensive patients treated with guanethidine show quite consistent variations in blood pressure at different times of the day the pressure is lower in the morning than in the afternoon or evening and exercise causes a much greater fall in pressure in the morning than later in the day This is of some practical importance since it may not be possible to control the level of blood pressure in the afternoon without causing serious hypotension in the morning

This variation is not seen in untreated hypertensive patients and it is almost certainly not due to changing concentrations of the drug in the circulation Guanethidine is very slowly excreted and hypotension occurs in the morning whether the drug is given in a single dose in the morning or the evening or in divided doses through the day Since it is known that patients who have had surgical or chemical sympathectomies are unable to maintain their arterial pressures in the face of relatively small losses of blood the plasma volume was examined at different times of the day in untreated hypertensive patients and in patients receiving guanethidine or other hypotensive agents With few exceptions measurements were made on clinic patients who were performing their normal daily tasks without any dietary restriction

Plasma volume was measured using I human serum albumin Measurements made at the same time on two consecutive days showed a small variation in normal and hypertensive subjects The second estimation averaged 100.9 per cent S D ± 3.4 per cent of the first

Plasma volumes were then measured at 9-9:30 A M and at 4-4:30 P M in 10 normal subjects 9 untreated patients with severe hypertension 10 hypertensive patients treated with guanethidine alone 9 patients treated with guanethidine in combination with a benzothiadiazine diuretic and 7 hypertensive patients treated with other drugs In the normal subjects the plasma volume was slightly greater in the afternoon than in the morning (average 103.7 S E ± 1.7 per cent) In the four groups of hypertensive patients the plasma volume in the afternoon was considerably greater than that in the morning for untreated patients the plasma volume in the afternoon as a percentage of that in the morning averaged 112.8 S E ± 1.7 per cent In the three treated groups the afternoon plasma volumes averaged 111.6 S E ± 2.7 per cent 110.8 S E ± 2.0 per cent and 112.9 per cent respectively of the morning values Changes in blood volume calculated from corrected hematocrit values were similar although slightly smaller in degree since there was a tendency for the packed cell volume to decrease during the day

This increase was independent of the order of measurement and there was no evidence of impaired or delayed mixing of indicator in the morning estimations to account for the variation None of the patients showed clinical evidence of cardiac failure The treated hypertensive patients showed no significant change in blood pressure between morning and afternoon readings whereas all but one of the patients receiving guanethidine had a lower blood pressure in the morning than in the afternoon In 3 such patients changes in plasma volume and blood pressure were measured on one day Next day rapid infusion of the appropriate amount of plasma in the morning raised the blood pressure measured at rest or after exercise to levels similar to those found during the previous afternoon Thus it seems likely that morning hypotension in patients receiving guanethidine is at least in part a consequence of changing plasma volume The diurnal plasma volume pattern

unaffected by diuretics given at any time of the day and appears to be related to hypertension rather than to the drugs used to treat it. It is unlikely to be a consequence of changes in posture since the patients had risen at least 1½ hours before the morning estimation. Similar diurnal changes in plasma volume were observed in 6 hypertensive patients confined to bed but not in 3 bedfast subjects without hypertension.

The absolute level of blood volume in the hypertensive patients did not differ significantly from those in the normal subjects.

A diurnal variation in hemoglobin concentration was observed which correlated significantly with the observed changes in blood volume, although the change in hemoglobin concentration was less than that which would be predicted on the basis of dilution of a fixed quantity of circulating hemoglobin. Since the changes in blood volume were calculated from determinations of plasma volume and hematocrit, this may reflect a change in the ratio between venous and total body hematocrit rather than a change in the quantity of hemoglobin within the circulation. Plasma protein concentration did not change significantly during the day; discrepancies between hemoglobin and changes in plasma protein have been noted before,[2] and it is clear that changes in plasma protein concentration cannot be used as an indication of changes in plasma volume.

In the hypertensive patients with large changes in plasma volume there were no significant changes in weight or in the concentration of plasma electrolytes. It appears most likely, therefore, that the plasma volume changes at the expense of extravascular fluid, although this has not been established conclusively.

There is other evidence that hypertensive patients may regulate their blood volumes less precisely than do normal subjects. Blood volume is normally decreased when one changes from the recumbent to the erect posture. Wolf and Eisenberg[3] have shown that this decrease is greater in hypertensive than in normal subjects.

It is unknown whether the instability of vascular volume is a consequence or a cause of hypertension, and the mechanisms responsible are equally obscure, although relative changes in precapillary and postcapillary vascular tone[4] might be the cause. Whatever the mechanism, it is not easy to decrease these changes in blood volume, and the practical problem of controlling blood pressure at all times of day is some distance from solution in patients receiving guanethidine.

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The heart in hypothyroidism

Clinical experience and pathologic observations indicate that lesions of the myocardium and pericardial effusions[1-4] undoubtedly occur in uncomplicated hypothyroidism. However, the exact cause of these cardiac lesions and the nature of the associated hemodynamic disturbances have challenged clinicians and physiologists for more than half a century.

In establishing the [illegible] evidence of [illegible] early [illegible] dominant symptoms [illegible] absent or [illegible] the diagnosis of *myxedema heart* [illegible] the [illegible] electrocardiographic [illegible] low-voltage QRS complexes, prolongation of the P-R and Q-T intervals, and flattening of the T waves) without symptoms or signs of heart failure or evidence of cardiac enlargement on the chest radiograph, or when, in the presence of the aforementioned classic electrocardiographic pattern, patients *appear* to be in early heart failure (elevated jugular venous pressure, mild edema of the ankles, and moist sounds at the lung bases) [illegible] mild or [illegible] degree of cardiomegaly.

[illegible] Such patients [illegible] over 60 [illegible] hypertension [illegible] coronary artery disease [illegible] Furthermore [illegible] ECG [illegible] left ventricular hypertrophy [illegible] coronary artery disease rather than the classic pattern of myxedema.

It would seem, therefore, that the often stated belief that myxedema predisposes to premature coronary artery disease and generalized atherosclerosis may be incorrect.

Since pathologic material is rarely obtained from patients with a mild degree of hypothyroidism, accurate histologic interpretation of the early, uncomplicated cardiac lesions has proved to be difficult, and opinions differ with regard to both the nature and incidence of myocardial and pericardial involvement at this stage. In the more advanced case, autopsy sometimes reveals marked cardiac enlargement with gross dilatation of all chambers but with little, if any, hypertrophy of the ventricular walls. Microscopy shows vacuolation, loss of striation, and branching of the subendocardial fibrils, together with interstitial edema and patchy fibrosis of the ventricular walls. Mucoid infiltration of the myocardium has also been reported. However, the incidence, severity, and distribution of these lesions vary considerably. Furthermore, they do not appear to be specific for myxedema heart disease, since similar lesions have been described in beriberi and coronary artery disease.

Histologic evidence of pericardial damage has not been reported in myxedema, although more than a liter of fluid may collect in the pericardial cavity. However, the protein content of the fluid is known to be high (6 to 8 Gm. per cent) and the cell count is low.

These observations, together with (a) the recognized increase in systemic capillary permeability in myxedema and (b) the rapid resolution of both heart size and electrocardiographic abnormalities with improvement in capillary permeability after hormone therapy, strongly suggest that fluid collects in the pericardial cavity and between the muscle fibrils of the ventricular wall as a consequence of an abnormality of the capillaries.

Physiologic studies in uncomplicated and untreated myxedema have produced conflicting results. Some workers have shown that the cardiac output usually falls in parallel with the reduction in oxygen consumption (i.e., the arteriovenous oxygen difference remains normal) and that the intracardiac and pulmonary arterial pressures and pulmonary vascular resistance are within the normal range. In addition, recent work indicates that the central blood volume is not increased in myxedema. However, in other studies and in individual reported cases, the mixed venous arteriovenous oxygen difference was found to be increased or the intracardiac pressures were observed to be raised. The latter finding has been attributed to the restrictive effect of a recognized or unrecognized pericardial effusion, and only rarely to evidence of heart failure when associated with an increase in the arteriovenous oxygen difference. It should be remembered, however, that if myocardial compliance is greater than normal, as might well be the case in myxedema heart disease, the conventionally accepted ranges of intracardiac pressures could still be found in the presence of heart failure. Furthermore, small collections of pericardial fluid accumulating slowly would not be expected to cause significant restriction to cardiac filling and therefore cannot adequately explain the observed rises in intracardiac pressures reported under these circumstances. Thus it would seem that clinical evidence of cardiac failure in uncomplicated hypothyroidism is probably uncommon. On the other hand, we believe that in the presence of coincidental cardiac disease (hypertension, coronary artery disease, rheumatic heart disease), myxedematous heart damage can undoubtedly precipitate heart failure, even though paradoxically, in some patients with normal thyroid function, antithyroid drugs can be helpful in treating intractable heart failure or angina pectoris by reducing the demands on oxygen transport.

To date, no satisfactory explanation of the classic electrocardiographic pattern of myxedema heart disease has been offered, although it seems highly probable that fluid in the pericardial cavity and/or interstitial myocardial edema account for the observed electrical abnormalities.

In conclusion, it would appear that there are several cardiovascular problems to be resolved in hypothyroidism. In particular, further comprehensive hemodynamic, angiocardiographic, and metabolic studies are required in those patients who have little or no cardiac enlargement, yet whose electrocardiograms demonstrate the classic pattern of myxedema heart disease.

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Book reviews

Electronic and Computer Assisted Studies of Bio-Medical Problems. Edited by Otto H. Schmitt, Ph.D., Professor of Biophysics, University of Minnesota, Minneapolis, Minn., and Cesar A. Caceres, M.D., Chief, Instrumentation Unit, Heart Disease Control Program, U.S. Public Health Service, and Assistant Clinical Professor of Medicine, George Washington University Hospital, Washington, D. C. Springfield, Ill., 1964, Charles C Thomas. 314 pages. Price $12.50.

According to its preface, This volume is a verbatim transcript of a 3-day meeting to examine prospects for the development of electronic computers and related equipment to aid the life sciences. Thirty-four persons well known in medicine and biomedical physics and engineering participated in the conference.

The transcript makes interesting reading. Brief and lively discussion replaced long papers. If the reader is looking for solutions to his immediate problems, he will be disappointed; if he wants to know the thoughts of his fellow investigators on the present and future status of electronic computing and magnetic tape recording systems in biomedical studies, he will be pleased. Cardiologists will be especially interested because most of the discussion revolved about the ECG and the VCG.

The excellent foreword by Dr. Schmitt, moderator of the meeting, should be required reading. The chapters of the book are entitled: (1) The electrocardiogram as subject matter for electromedical computer studies, (2) Applications of automation to the electrocardiogram, (3) Problems concerning arrhythmias, (4) The art and science of magnetic tape recording systems for bio-medicine, (5) Computer instrumentation, (6) Models for modular and specialized biomedical computers, (7) The philosophies for bio-medical computation.

The discussions covered such subjects as limitations of the dipole theory in ECG, objectives of machine analysis in diagnosis and prognosis, data storage, acquisition and retrieval systems, the analog to digital converter, the cost of an ideal laboratory computer, and analog versus digital processing.

An excellent index facilitates use of the book.

The Lung and Its Disorders in the Newborn Infant. By Mary Ellen Avery, A.B., M.D., Assistant Professor of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, Md., and Alexander J. Schaffer, Consulting Editor. Volume I in the series Major Problems in Clinical Pediatrics. Philadelphia, 1964, W. B. Saunders Company. 224 pages. Price $7.50.

In 200 pages Dr. Avery has put together a very concise but complete fashion a discussion of the lung and its disorders in the newborn infant. The normal development and physiology of the fetal and neonatal lungs is well covered and includes a wealth of recent information. Disorders of respiration in the newborn infant are approached mainly from the point of view of the clinician who is most concerned with the care of such infants. Dr. Avery has given particular attention to hyaline membrane disease, a disorder on which she is a world authority, and rightly so. Her treatment of this section is outstanding and should be read by all who care for babies with the condition. Finally, the author discusses in detail the various factors to be considered in resuscitation of the newborn infant, including the use of respirators and various types of masks.

The book is very easy to read. The illustrations are of top quality and are very helpful in understanding the points under discussion.

Intracardiac Auscultation and Phonocardiography. By Giorgio A. Feruglio, M.D., Research Associate and Instructor in Cardiology, University of Ferrara; Ospedale Civile, Udine, Italy. Turin, 1964, Edizioni Minerva Medica. 133 pages.

This book is concerned with the technique, findings, and interpretation of intracardiac phonocardiography. Although highly specialized from the point of view of the practicing physician, the book should interest those working on the subject and those concerned with the mechanisms and origins of normal and abnormal heart sound. The illustrations are good, although the discussions are brief. Even though intracardiac methods have their shortcomings, this book should be of value to those interested in phonocardiography.

The Armed Forces Institute of Pathology: Its First Century, 1862-1962. By Robert S. Henry, A.B., LL.B., Litt.D. Washington, D. C., 1964, U. S. Government Printing Office. 422 pages. Price $4.75.

This book describes some of the outstanding contributions made in medicine by various people working in the Armed Forces Institute of Pathology during its first century of existence. The centennial year ended in 1962. Needless to say, the Institute of Pathology has made many important contributions too numerous and often too immeasurable (or even unknown) to be described in this 400-page book.

Mr. Henry describes the development of the Institute from the time of its organization during the days of the Civil War, when there was sickness and injury among the soldiers of America of a magnitude never encountered before in this country, and he describes the need for organizing the Medical Department of the Army. This was done by Congress and the bill signed by Abraham ... 1862. The new Surgeon

General of the Army Alexander Hammond organized the Army Medical Museum through which the Armed Forces Institute of Pathology developed. The Institute is now one of the most important institutions in the world. Its leaders have fostered a scientific atmosphere, have recognized the responsibilities of the Institute and have approached and solved many important problems in the field of public health and medicine. Among a few prominent men from the Institute who have contributed to world health are Walter Reed, Agramonte, Finlay, Lazear, Gorgas, Carroll, Russell and many others.

Henry has done an excellent service to the Institute and medicine in writing this book. The format is excellent, the composition lucid, the illustrations are clear, simple and numerous and the index is good. This valuable book should interest not only pathologists but all people in medicine. It clearly indicates the tremendous accomplishments of a military organization under vigorous leadership and support.

FERMENTDIAGNOSTIK INTERNER ERKRANKUNGEN (Enzyme Diagnosis in Internal Medicine). By Dr. Diethard Amelung, Privatdozent I. Medizinischen Klinik der Medizinischen Akademie Düsseldorf. Stuttgart, 1964, Georg Thieme Verlag, 179 pages.

This concise and well written book (179 pages, 37 figures and 12 tables) outlines diagnostic interpretation of serum enzyme changes in a number of diseases. The author discusses the common enzyme methods as well as some new ones that are useful in internal medicine. Not all diseases are included which could be recognized by enzyme diagnosis. However, the disorders considered are evaluated in the light of numerous up-to-date references. For example, in diagnosing various liver diseases multiple parameters are used simultaneously throughout the course of the disease.

This book is highly recommended for the internist who has ready access to the proper laboratory.

THE STREPTOCOCCUS, RHEUMATIC FEVER AND GLOMERULONEPHRITIS. Edited by Jonathan W. Uhr, M.D., Associate Professor of Medicine, New York University School of Medicine, New York, N. Y. Baltimore, 1964, Williams & Wilkins Company, 419 pages. Price $7.50.

This latest basic work on streptococci is well collated and provides a needed addition to the library of the serious student of group A streptococci and the non-suppurative complications caused by these organisms. Because the level of presentation is high, the average clinician will find the going difficult.

The conference is divided into three major areas: one relates to the organism, the second to the host, and the third to the relationship between the two. The information itself is generally available in individual publications but an excellent review can be obtained from this single volume.

McCarty describes his latest observations on the rhamnose and glucosamine composition in relation to the immunological responses of group A and C organisms and several recently discovered variant strains. The activity of phages (both virulent and temperate) has been neglected generally, but available data are brought up to date by Maxted, while Zabriskie approaches the phage problem by attempting to relate lysogeny to the production of erythrogenic toxin.

Halbert's exquisite separation of various extracellular components raises some very pertinent questions. Our current concept of pathogenicity as related to the intracellular M protein is at least open to question. The whole idea of preparation of vaccines from M proteins should be reconsidered in regard to whether extracellular components should be added or substituted.

The streptococcal deoxyribonucleases are clearly demonstrated by Wannamaker to be of four different types, thus explaining some peculiarities of behavior not previously understood.

In the section on host responses the cross reaction between heart tissue and group A streptococcal cells has been demonstrated. The immunofluorescent studies of Kaplan are very promising and one may hope that future studies will show that a greater percentage of rheumatic hearts are reacting positively to the appropriate streptococcal antisera.

The multinodular skin reaction of rabbits to the injection of sterile extracts of sonically disrupted group A streptococci is suggested by Comartie as an experimental model for understanding the pathogenesis of streptococcus-related diseases.

By microscopic comparison Murphy demonstrates lesions in rabbit heart after repeated infections with streptococci of different groups which he believes are identical to the Aschoff bodies of rheumatic fever in human beings. His arguments are most logical and attractive as are his responses to those disagreements which have been presented.

Tan reviews past experiences with attempts to produce experimental glomerulonephritis by injection of streptococci or streptococcal product but cautions that no laboratory model has yet been developed which resembles the post streptococcal acute glomerulonephritis in human beings. Dixon and Feldman describe attempts to produce such lesions by immunological techniques and favor the conclusion that circulating antibody probably plays no role although sensitized cells may.

The general problem of pathogenesis of collagen diseases as related to autoimmunity is reviewed by Thomas. He cautions that the antibody findings may be an effect rather than a cause. The possible part played by lysosome enzymes is also described.

The third division of the volume relates to epidemiologic and clinical aspects. Rammelkamp reviews the evidence for certain type-specific

strains of group A streptococci being ... lved in the pathogenesis of human glomerulonephritis.

The correlation between magnitude of immunologic response to untreated group A streptococcal infection and attack rate of rheumatic fever is stressed by Stollerman. The persistence of the organism in the throat is of significance. Certain clinical features of pharyngitis (exudate, high fever, high white blood cell count) are commonly associated with rheumatic fever. These findings affect the rates of secondary as well as initial rheumatic attacks.

Epidemiologically, Taranta brings clinical concepts up to date. Two salient features in his review refer to the repetitive syndrome in recurrence and the antistreptococcal therapeutic approach of Rammelkamp as a means of treatment of acute rheumatic fever.

Good and Gabrielsen review agammaglobulinemia (more properly termed hypogammaglobulinemia). They describe a clinical picture of disease which is similar to rheumatoid arthritis but which differs from the latter in response to gamma globulin therapy. Hypogammaglobulinemia respond to such treatment, whereas rheumatoid arthritis does not.

The volume is disappointing to the hope that completely new approaches to the entire problem of rheumatic fever and glomerulonephritis might have appeared on the horizon. Only minimal mention is given to such subjects as heredity and genetics. The discussion of enzyme activities might have been broadened.

Cardiovascular Surgery 1963. Edited by F. A. Simeone, M.D., Professor of Surgery, Western Reserve University, Cleveland, Ohio. New York, 1964, American Heart Association. 160 pages.

This monograph, prepared under the auspices of the American Heart Association, contains papers presented before the Council on Cardiovascular Surgery at the 1963 Scientific Sessions of the American Heart Association.

The 30 papers contained in this volume give a good idea of the investigative interest of American cardiac surgeons at this time. There is a fairly broad distribution of subject material. The first four papers are concerned with total replacement of various cardiac valves with the caged ball type of prosthesis. Three papers are concerned with autotransplantation or homotransplantation of valves or the entire heart. Six papers are concerned with surgical treatment of forms of congenital heart disease for which entirely satisfactory treatment is not currently available or about which there is no consensus regarding the most desirable surgical technique to be employed (truncus arteriosus, transposition of the great vessels, subaortic hypertrophic stenosis). There are only three papers concerned with all aspects of peripheral vascular disease. This probably reflects accurately the current status in surgical investigation of this area. This monograph will probably find its place primarily in libraries where it can be used as a source of reference. It will be of value almost exclusively to cardiac surgeons.

Innervation der Venen (Innervation of the Veins). By Dr. Med. B. A. Dolgo-Saburow. Berlin, 1963, Veb Verlag Volk und Gesundheit. 308 pages.

This book reveals very well the important contributions that can still be made by experimental morphologic techniques. The veins are extremely important structures which have not received the attention they deserve. The book summarizes studies of the innervation of veins. The illustrations are very good. The author is from Leningrad and his bibliography is mainly of Russian work. This book is recommended not only to those who are interested in veins but to all who are interested in the peripheral circulation. The bibliography provides a good collection of references to Russian papers.

Second European Conference on Microcirculation, Pavia 1962. Edited by H. Harders, Hamburg. Basel, 1964, S. Karger. 739 pages. (American representative: Albert J. Phiebig, P. O. Box 352, White Plains, N. Y.) Price $51.

This is a very good summary of the proceedings of the Second European Conference on Microcirculation held in Pavia in 1962. The volume contains over 100 papers of varying length and covering many subjects related to the microcirculation by experts from all parts of the world. The papers deal with the usual problems discussed at any meeting concerned with the microcirculation, but a large number of papers in this volume describe studies in rheology, with particular emphasis on viscosity, hematocrit, and shear rate and shear stress. The proceedings are well prepared so that the volume should be of considerable value to those interested in the problem even though they did not attend the conference. It should be especially valuable to any one interested in the peripheral circulation. The authors, with the apparent approval of the editing staff, used abbreviations freely throughout their papers. This practice annoys the reader and makes the reading and absorbing of the material a slow and even laborious process. Despite the fact that those responsible for the proceedings did not attain the ultimate in reporting, it is still a good and very worth while report.

Announcements

The American College of Cardiology will present SYMPOSIUM ON OPERABLE HEART DISEASE at the University of Kentucky Medical Center Lexington Ky on Sept 24 and 25 1964 The symposium is sponsored by the Kentucky Heart Association and the University of Kentucky College of Medicine Inquiries should be directed to American College of Cardiology Empire State Bldg New York N Y 10001

NATIONAL TUBERCULOSIS ASSOCIATION FELLOWSHIPS The medical section of the National Tuberculosis Association the American Thoracic Society provides fellowships for the graduate education of investigators and teachers in the field of respiratory diseases and tuberculosis The following types are offered

Research Fellowships Postdoctoral fellowships are offered to candidates holding the degree of M D Ph D or Sc D for further training as scientific investigators *Predoctoral fellowships* are offered to graduate students with a bachelor s or master degree to work on a research project for an advanced degree other than an M D

Teaching Fellowships Physicians entering their second or third year of residency in internal medicine pediatrics thoracic surgery or other specialty at a medical center are offered fellowships for training directed toward a career of medical school teaching in pulmonary disease

Edward Livingston Trudeau Fellowships A few fellowships are offered to young physicians who have completed their hospital residency training and are now ready to assume responsibility for medical school teaching programs They must be assured of teaching or research faculty appointment

Each applicant for an NTA Fellowship must have been accepted by the head of the department under whom he expects to work for the next academic year in a medical center or hospital in this country

Awards are determined by individual circumstances and are paid directly to the Fellow on a quarterly basis

Fellowships may begin on any date after April 1 Research and teaching fellowships are renewable for a total of 3 years and Edward Livingston Trudeau fellowships for 4 years

All applications must be submitted by November 1 Further information about fellowships may be obtained upon request from Director of Medical Education American Thoracic Society 1790 Broadway New York N Y 10019

The Division of Continuing Education of The University of Texas Graduate School of Biomedical Sciences at Houston will present a course on RECENT ADVANCES IN CARDIOVASCULAR DISEASES on Dec 7 8 and 9 1964 in the Texas Medical Center Houston Texas Dr Victor A McKusick Professor of Medicine The Johns Hopkins University School of Medicine Baltimore Md will discuss genetics heritable disorders of connective tissue and cardiovascular sounds and murmurs

For further information write Division of Continuing Education The University of Texas Graduate School of Biomedical Sciences at Houston 107 Jesse Jones Library Bldg Texas Medical Center Houston Texas 77025

A seminar on the TREATMENT OF COMPLETE HEART BLOCK sponsored by the Vermont Heart Association and the University of Vermont College of Medicine will be held at the DeGoesbriand Memorial Hospital Burlington Vt on Oct 10 and 11 1964

In addition to the regular members from the College Samuel Bellet M D (or co worker) William M Chardack M D Gordon K Moe M D and Paul M Zoll M D will participate as guest speakers

Further information can be obtained from Eugene Lepeschkin M D Cardiovascular Research Unit DeGoesbriand Memorial Hospital Burlington Vt

CURRENT PRACTICAL ASPECTS OF CARDIOVASCULAR DISEASES a one day symposium will be presented by the Division of Continuing Education of the University of Texas Graduate School of Biomedical Sciences at Houston and the Frederick I Lummis Medical Foundation on Oct 31 1964 in the Texas Medical Center Houston Tex

This course is intended to give practicing physicians a useful and authoritative review of current medical and surgical approaches used in managing common cardiovascular problems in adults Credit for attendance will be given by the American Academy of General Practice

Topics to be discussed are Changing concepts in ischemic heart disease hypertensive vascular disease diagnosis and chronic medical management clinical approach to strokes management of hypertensive emergencies and other special situations acute and chronic management of strokes rheumatic heart disease in adults current concepts management of cardiac arrhythmias by cardioversion indications for surgery in arteriosclerotic diseases the surgical treatment of mitral and aortic valve lesions

Participating guest speakers are E Harvey Estes Jr M D Department of Medicine Duke University Medical Center James Conway M D Hypertension Unit University of Michigan Medical Center Clark H Millikan M D Department of Neurology Mayo Clinic John M Lewis M D Department of Medicine Baylor University College of Medicine Stanley Crawford M D Department of Surgery Baylor University College of Medicine and Denton A Cooley M D Department of Surgery Baylor University College of Medicine

For further information write Division of Continuing Education University of Texas Graduate School of Biomedical Sciences at Houston 107 Jesse Jones Library Bldg Texas Medical Center Houston Tex 77025

American Heart Journal

October 1964 Volume 68 Number 4

Editorial

Cardiac edema

*Douglas A. K. Black, M.D.**
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Faced with a blank page and the (self chosen) subject of cardiac edema, one's first instinct is to justify the choice of a topic on which it might well appear that everything conceivable within the limits of present knowledge has been said. But the familiar as well as the rare has its challenge, and the very extensive resources available to us for the palliation of cardiac edema may constitute a dangerous pragmatic excuse for neglecting the persistent enquiry into causes and mechanisms which is the basis of radical progress. As a general physician with an interest in body fluid, I would not usefully deal in a cardiological journal with the many diseases which can lead to the syndrome of cardiac edema, nor would this be a proper place to review the diuretic palliation of edema. As a student of mechanism, I would offer instead some comment on the nosology of cardiac edema, the role of aldosterone, and the hyponatremic state.

As Himsworth[1] pointed out, the value of the concept of a syndrome consists in precisely this evasion, that we can concentrate on physiologic mechanism leaving aside etiology. Although it is no doubt quite proper to use "syndrome" as a term for a complex of symptoms found in a single disease, there seems little to gain by doing so, and the term "symptom complex" must seem just as good, leaving "syndrome" free to denote a recognizable clinical picture of multiple etiology. In the case of cardiac edema, undeniably a syndrome on these terms, the matter does not end there. Even apart from the obvious clinical distinction between the pulmonary edema of predominantly left heart failure and the peripheral edema of predominantly right heart failure, there is a range of biochemical variation, in part iatrogenic, which sometimes reflects itself in altered concentrations of serum electrolytes. But not necessarily so, since a normal serum potassium does not exclude a state of potassium depletion sufficient to potentiate the action of a previously appropriate dose of digitalis to the level of dangerous toxicity, for example, paroxysmal atrial tachycardia with partial heart block. To these examples of clinical and biochemical variation there can certainly be added gross hemodynamic variation, as implied in the terms "forward" and "backward," and "low output" and "high-output" failure. The diversity of the functional impairment underlying cardiac edema in different patients scarcely needs stressing; it is mentioned here by way of *caveat* against expecting any simple and comprehensive explanation of cardiac edema. More shortly, we are probably concerned

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with several syndromes masquerading as one.

To exemplify this point, let us look at the role of aldosterone in the pathogenesis of cardiac edema. Nothing could better illustrate the truism that major discoveries do not "solve problems," but they alter the manner in which problems are to be considered, and in so doing, they expose a wider perimeter of inadequate knowledge. The discovery that almost all the salt-retaining activity of adrenal hormones can be accounted for by aldosterone has indeed refined our analysis of the situation; the availability of semiquantitative assay methods for excretion, secretion,[5] and plasma concentration[6] of aldosterone allows us to judge whether the aldosterone mechanism is playing a major or a negligible role in different states of edema. In the hypoproteinemic forms of edema (nephrosis, cirrhosis, protein-losing gastroenteropathy) the available evidence is that the aldosterone mechanism is active, even before the initiation of such therapeutic measures as salt restriction which are in themselves stimulants to aldosterone secretion. When protein depletion and the consequent hypovolemia can be corrected, the aldosterone mechanism becomes less active. Renal retention of salt occurs not only in low-output but also in high-output failure, and these two states have in common a state of renal ischemia. This perhaps supports the concept of renal ischemia as the important stimulus to the aldosterone mechanism, rather than hypovolemia per se or changes in output or alteration in electrolyte concentration.

But the picture of aldosterone activity in cardiac edema is less clear cut than in the hypoproteinemic edemas. An increase in the plasma level[6] or secretion[10] of aldosterone is inconstant in cardiac edema. And when present, it could be related to the therapeutic restriction of salt, to delayed hepatic inactivation of aldosterone,[11] or to protein depletion from inadequate diet or from loss of protein in the congested alimentary tract. Taken in conjunction with the well-known absence of edema in Conn's syndrome, these considerations cast considerable doubt on the primacy of the aldosterone mechanism in the sodium retention of cardiac failure. Further progress here clearly calls for the use of aldosterone assays in patients in the onset stage of cardiac failure, in whom the clinical documentation is adequate to disclose the defined causes of secondary aldosteronism. On a more practical level, the general use of aldosterone antagonists in the treatment of cardiac edema is plainly not justified; their use should be limited to those few patients in whom they can be shown to be effective in increasing the urinary output of sodium.

When cardiac edema is slow to clear and diuretics seem less effective, analysis often discloses a low concentration of sodium in the serum, loosely known as "hyponatremia" (the looseness consists in the verbal substitution of "blood" for "serum," and in the confusion of concentration and total amount). In these matters of communication, convenience generally prevails over strict accuracy—or, as some would say, bad coin drives out the good. So we talk of hyponatremia and hyponatremic. The general factors which govern the concentration of sodium in the serum have been ably reviewed by Leaf.[7] In the specific situation of cardiac edema, the presence of edema itself rules out an overall sodium depletion as the cause of hyponatremia. There can, however, be a central oligemia based on vigorous measures to deplete sodium, even in the continued presence of peripheral edema; this is the original "low salt" syndrome described by Schroeder,[12] which is marked by azotemia that may respond to cautious sodium repletion. In the great majority of patients with the combination of cardiac edema and hyponatremia, there is no evidence of oligemia and no useful response to hypertonic saline. The persistence of hyponatremia implies a failure of the kidneys to form an appropriately dilute urine, and this abnormality of renal function is currently receiving more attention in the pathogenesis of hyponatremia than is the alternative concept of a shift of sodium into damaged cells—the essentially unprovable notion of a "sick-cell syndrome." Applicable in the case of cardiac edema are considerations similar to those which have led Schwartz and his colleagues[13] to hypothecate "inappropriate secretion of antidiuretic hormone" as an explanation

of the hyponatremia seen in advanced neoplastic disease. An excess of ADH cannot account for edema but it is an adequate explanation of hyponatremia.

The mechanism underlying inappropriate secretion of ADH in these hyponatremic states has not, however, been uncovered, and so it is worth noting that an excess of ADH is not the only possible cause of the inappropriate formation of concentrated urine. Berliner and Davidson[15] made the critical observation that constriction of one renal artery during water diuresis in dogs could lead to the formation of concentrated urine from the ischemic kidney, whereas the continuous absence of ADH was attested by the persistent formation of dilute urine from the other kidney. The formation of hypertonic urine largely depends on a hyperosmotic zone in the renal medulla established by the active transfer of sodium from the lumen of the ascending limb of Henle's loop into the interstitial tissue.[16] Although severe limitation of blood flow could lead to the arrest of sodium transfer, moderate limitation of blood flow could even increase medullary hyperosmolality by decreasing the washout of solute from the medulla.[17] It seems possible that in certain stages of cardiac failure the restriction of medullary circulation might be of an order to enhance osmolality and so allow the formation of concentrated urine even in the presence of hyponatremia.

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Clinical communications

Normal redundancy in chest leads as basis for recognition of minor abnormalities

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There is a redundancy of electrocardiographic information in the conventional chest leads, as may be expected theoretically and as is shown in the continuity of trends of QRS and T amplitudes across the chest (Simonson,[1] Figures 13-15). Consequently, it has been suggested in conferences on epidemiology of heart disease to limit the chest leads to three. We make the opposite suggestion, to utilize the normal redundancy for prediction of abnormality. This involves the question of localized potentials. The redundancy is based on the dipole source of differences in ECG potential, and it is of secondary importance for this study whether a single shifting dipole or two or multiple dipoles are assumed. Localized potentials recorded in one or the other lead could not be predicted from other leads. The literature on localized potentials is extensive and controversial[1] and cannot be reviewed here in detail. We limit ourselves to two apparently somewhat contradictory findings: in normal subjects about 10 per cent and in cardiac patients about 20 per cent of cardiac potentials were not cancellable and thus not referable to a dipole source.[2,3] On the other hand, Pipberger and associates[4] were able to reproduce all abnormalities in conventional chest leads from corrected orthogonal leads by means of a converter.

In the conventional electrocardiographic interpretation, usually the normal limits for single leads are employed. A break in the continuity of the trend of QRS and T deflections across the chest may be the earliest recognizable sign of developing abnormality. However, there was so far no precise statistical basis for such prediction. The purpose of this study is to provide such basis.

Sample. The sample consisted of 640 healthy men who ranged in age from 20 to 59 years. Most of the men were railroad employees† distributed in middle and northwestern states over a wide geographical area; in addition, students of the University of Minnesota and employees of the Mutual Insurance Companies, St. Paul, Minnesota, were used for the younger age groups.‡ The screening was done on the basis of a thorough routine clinical examination, history, and laboratory tests.

Excluded were subjects with objective

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†The material was collected under the supervision of Dr. H. L. Taylor, supported by National Institute of Health Grant HE [illegible].
‡Collected by Dr. H. W. Blackburn, Jr.

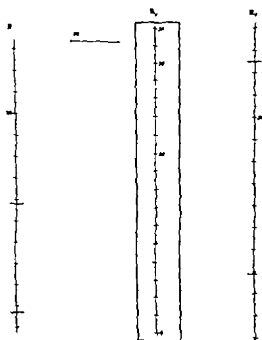


Fig 1 Mark the measured amplitude of R and R on their respective scales Connect these two points with a straight line The point at which this line crosses the scale for R is then the predicted value of R The standard error as indicated by the length of the bar projected on the graph of R_{V_4} is 5 5 mm If the actual value of R is within 5 5 mm from the predicted value the amplitude should be considered to be normal

evidence of or suspected coronary heart disease gross ECG abnormalities (such as myocardial infarct pattern) arterial hypertension renal disease any type of heart disease hypothyroidism or thyrotoxicosis diabetes convalescence after infectious diseases active gall bladder disease peptic ulcer pulmonary disease and organic or emotional disorders of the central nervous system A more detailed listing of the criteria for screening was given previously [1]

Results

Twelve conventional leads were taken but for practical reasons the analysis is limited to the chest leads V_1 to V_6 Regression equations were obtained by means of electronic computers for prediction of R and T for Lead V_4 from V_3 and V_5 for Lead V_5 from V_4 and V_6 and for Lead V_6 from V_5 (for R) and from V_5 and Lead I (as substitute for V_7) for T The regression equations with correlation coefficients (r) and standard errors (S E) are shown in Table I

The correlation coefficients are so high that a prediction of R and T deflections

Table I Regression equations for prediction of R and T waves in V_4, V_5 and V_6 from two adjacent leads in a sample of 640 normal men (ages 20 59 years)

Regression equation	r	S E
T_{V_4} = 114 + 708 R_{V_3} + 496 R_{V_5}	87	2 80
R = 745 + 831 R_{V_4} + 314 R	92	1 88
R_{V_6} = 1 234 + 666 R	86	1 87
T = − 173 + 697 T + 475 T_{V_5}	93	80
T_{V_5} = − 076 + 775 T_{V_4} + 348 T	97	64
T = 066 + 531 T + 214 T	88	55

r = Correlation coefficient S E = Standard error

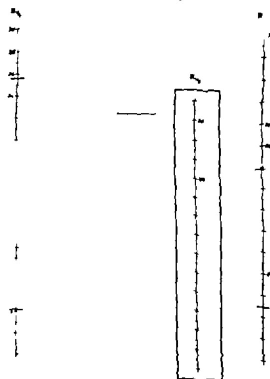


Fig Similar Fig 1

be so high that R and T waves are predictable with high probability from two adjacent leads by means of regression equations Thus abnormality can be predicted as a break in the continuity of the QRS and T deflections across the chest even if any single lead is within normal limits For easy clinical application a set of nomographs was constructed

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The transmission of systolic murmurs from the pulmonary artery into the left atrium

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Intracardiac phonocardiography has been studied in man for the past 10 years.[1] During that time the intracardiac acoustical events associated with most types of heart disease have been described.[1]

Investigators have reported that heart murmurs are localized in the chamber or vessel which receives the flow of blood responsible for the production of the murmur. For example, in the case of ventricular septal defect the murmur is recorded from the right ventricle. However, little mention has been made of transmission of heart sounds and murmurs from one chamber to another. Most reports emphasize that murmurs which are recorded from one chamber are not present in other chambers.

Discussions concerning the presence and significance of murmurs recorded from the atria are few.[3-11] This is especially true of the left atrium. Lumada and Liu[4] have reported regurgitant systolic murmurs in the left atrium associated with mitral insufficiency. Lewis and associates[5] have recorded murmurs from the pulmonary veins and adjacent areas of the left atrium in association with intense murmurs in the pulmonary artery. They postulate the transmission of sound in the blood flowing from the pulmonary arteries through capillaries and back through the pulmonary veins into the left atrium as the mechanism of production of these murmurs. Sears, Movafagh, and Manning[10] have suggested that systolic murmurs may be transmitted from the right pulmonary artery directly into the *right* atrium.

Recently, Beuren and Apitz[2] described direct transmission of systolic murmurs into the *left* atrium from the pulmonary artery in patients with valvular pulmonic stenosis and from the aorta in patients with supravalvular aortic stenosis. Their findings, as mentioned in their paper, require further substantiation.

The purpose of this paper is to report

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that all murmurs which are recorded from the left atrium do not necessarily originate in that chamber. It confirms the observation that murmurs may be transmitted directly into the left atrium from the adjacent vessels.

Method and materials

Cardiac catheterization in infants and children provides an opportunity for study of the left atrium since the phonocatheter may be passed with relative ease into that chamber through the probe patent foramen ovale as well as through an atrial septal defect.

Intracardiac phonocardiograms were obtained during 115 consecutive cardiac catheterizations in infants and children at St. Christopher's Hospital for Children. The left atrium was entered in 26 of these subjects. The phonocardiograms recorded in the left atrium were analyzed to determine the presence of murmurs.

The intracardiac sounds were recorded using the intracardiac micromanometer of Allard Laurens.[1] The manufacturer states that there is a response from 2,500 cycles per second to direct current with this transducer. By means of filters frequencies less than 40 cycles per second are displayed as pressure and those over 40 cycles per second are displayed as sound. Thus sound and pressure are recorded simultaneously from the tip of the same catheter. A second pressure tracing may be recorded by connecting the side lumen which is 15 mm. proximal to the tip of the catheter to an external transducer. Recordings were made with a photographic recorder at speeds of 25 and 50 mm. per second. In the recordings illustrated in this paper only those made at 25 mm. per second are shown.

Results

A number of patients were found to have prominent left atrial systolic murmurs which were unassociated with specific left atrial pathology or mitral valve disease. This type of murmur was encountered

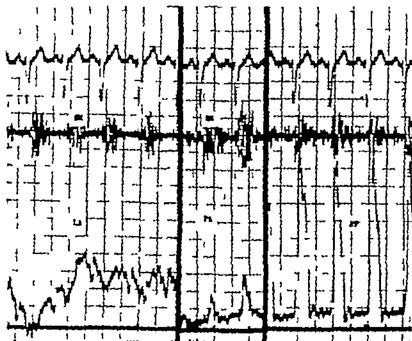


Fig. 1. Intracardiac phonocardiogram from patient with tetralogy of Fallot. Sound recorded in left atrial appendage (*LA*), pulmonary artery (*PA*), and right ventricle (*RV*). The left atrial pressure tracing is of greater sensitivity than the tracings from the pulmonary artery and the right ventricle. Note the similarity between the systolic murmur in the pulmonary artery and that in the left atrial appendage.

in the left atrial appendage only in patients with congenital heart disease associated with loud pulmonary artery murmurs

The left atrium was entered in 8 of 12 patients with tetralogy of Fallot. A systolic murmur was recorded from the left atrial appendage in 4 of these 8 cases. In each instance the murmur was localized to the area of the left atrial appendage adjacent to the pulmonary artery (Fig. 1) and disappeared in all instances upon withdrawal of the tip of the catheter into the body of the left atrium. The configuration, time of onset, and duration of the murmur from the left atrium were essentially the same as those of the murmur recorded in the pulmonary artery, but the intensity was less.

A murmur with characteristics similar to those of the murmur recorded in the pulmonary artery was found in 4 of 7 patients with atrial septal defect (Fig. 2) and in 3 of 3 patients with pulmonic stenosis in whom the left atrial appendage was entered.

The timing characteristics of the murmurs from the pulmonary artery and left atrial appendage were similar in all instances. The average interval between the onset of the QRS complex and the beginning of the murmur was 0.10 second in the pulmonary artery and 0.09 second in the left atrium. The duration of the murmur averaged 0.22 second in the pulmonary artery and 0.20 second in the left atrium.

Discussion

It is evident that the murmur in the left atrial appendage is due to the direct transmission of the murmur from the pulmonary artery. The intensity of the murmur in the left atrium is proportional to the loudness of the murmur in the pulmonary artery. The proximity of the left atrial appendage to the pulmonary artery and the similarity in the timing characteristics and configuration of murmurs from the two areas further supports a direct relationship between them.

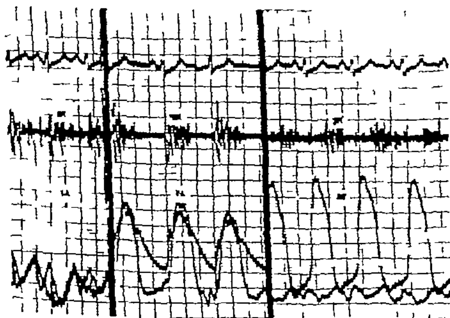


Fig. 2. Atrial septal defect. Sound recordings from the left atrial appendage (LA), pulmonary artery (PA), and right ventricle (RV). In the middle record the tip of catheter is in the pulmonary artery and the side lumen is in right ventricle. In the right hand record the tip of the catheter is in the right ventricle and the side lumen is in the right atrium. There is a systolic murmur in the pulmonary artery with transmission to the left atrial appendage. The diastolic flow murmur is located in the right ventricle distal to the tricuspid valve.

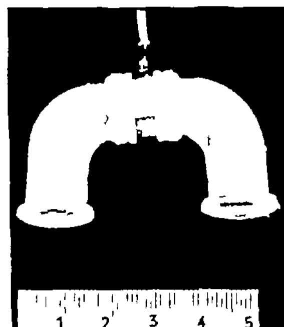


Fig. 1. A prosthesis made of silicone rubber for controlled [illegible] shunt. Centimeter scale.

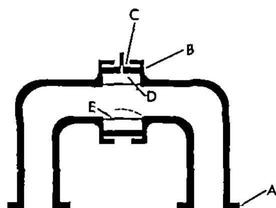


Fig. 2. Schematic presentation of the prosthesis. See text for description.

from the Lucite was a small metal nipple to which a length of polyvinyl tubing was attached. The flanges *B* were tightly applied around the Lucite tube by encircling sutures to provide an airtight space *D*, the volume of which could be regulated by injection through the polyvinyl tubing. The thin portion of the silicone tube *E* encased in the Lucite could be completely collapsed by injection of 0.8 to 1.0 ml. of fluid; withdrawal of the fluid resulted in wide opening of the tube to its full diameter of 8 mm. Thus the size of the communication could be controlled by means of this balloon device and in this way the shunt could be opened or closed to any degree in the closed chest animal, either anesthetized or unanesthetized.

The prosthesis was inserted between the descending aorta and main pulmonary artery in 42 mongrel dogs which weighed 18 to 23 kilograms. Under sodium pentobarbital anesthesia and positive pressure ventilation, a thoracotomy was performed in the fourth left intercostal space. The descending aorta just beyond the arch and the main pulmonary artery were mobilized by blunt dissection. An arterial clamp (Kapp-Beck coarctation clamp) was applied along a length of descending aorta to isolate this segment of the vessel from the circulating blood. A longitudinal incision was made into the lumen of the isolated segment and the flange of one limb of the shunt was sutured to the edges of the aortic incision by interrupted sutures. Similarly, the other limb of the shunt was sutured to the main pulmonary artery. The air in the lumen of the shunt was removed through a No. 27 needle, the shunt was partially closed, and the aortic and pulmonary clamps were removed.

Polyvinyl catheters were inserted into the aorta through the innominate or brachiocephalic artery, the left ventricle, left atrium, pulmonary artery, and right ventricle by methods described previously.[4] All catheters including the tube leading to the shunt were exteriorized at the back of the neck.

In 33 experiments, patterns of blood flow were recorded from sine-wave electromagnetic flow transducers (Kolin type)[5] which were placed around the ascending aorta (proximal to the shunt), the descending aorta (distal to the shunt), and the left pulmonary artery. In 2 experiments a flow transducer was placed around the prosthesis and contact with the blood was established by two fine stainless steel wires which projected through the wall of the prosthesis. In one animal a flow transducer was also placed around the brachiocephalic artery. The flow patterns were recorded on a Grass 8-channel direct writing oscillograph from which qualitative and directional changes in flow relative

to the control period could be measured readily.

All pressures were measured with Statham P23D pressure transducers. In 5 experiments cardiac output was determined by the Hamilton-Stewart principle using indocyanine green dye and sampling through a Gilson densitometer at the rate of 25 ml. per minute. When the shunt was closed, pulmonary and systemic flows were equal and cardiac output was determined from a dilution curve inscribed after injection into the pulmonary artery with sampling from the aorta. With the shunt open, pulmonary flow was estimated by injection into the left atrium with sampling from the aorta; systemic flow was calculated by injection into a peripheral vein with sampling from the right ventricle. The pressure tracings and dye curves were recorded on the Grass oscillograph. Hemoglobin oxygen saturation was measured in blood from the left atrium, pulmonary artery, and right ventricle with a Beckman Model B spectrophotometer by a modification of the technique of Gordy and Drabkin.[8]

In 2 experiments, a catheter tip transducer (Statham-Ford SF 1) was inserted into the aorta and left ventricle and into the pulmonary artery and right ventricle to overcome deficiencies in the response of the catheter-transducer systems in the critical analysis of timing of valve opening and closure events.

Results

The following is a description of the effects of opening and closing the shunt. The maneuver was performed in approximately 1 second and the diameter of the communication with the shunt open was 8 mm. Animals showed great individual variation in their ability to tolerate wide opening of the shunt. Some dogs rapidly developed pulmonary edema within 5 to 10 minutes, whereas others tolerated the shunt for several hours.

Heart rate and electrocardiogram. The heart rate increased by 10 to 40 per cent of the control value when the shunt was opened and returned to control levels after the shunt was closed. These changes occurred within 5 to 15 seconds. Frequently, one or more ventricular ectopic beats occurred as the shunt was opened and closed. No other significant changes were observed in the electrocardiographic pattern.

General responses of pressure and flow to opening and closure (Figs. 3 and 4, Table I). The immediate response to opening the shunt widely was similar in all animals, although the magnitude of the changes in pressure and flow varied greatly. The average changes in pressure immediately after the shunt was opened are summarized in Table I. The subsequent course of the blood pressures and flows and the response to closure of the shunt are described below.

Left ventricular and aortic systolic pressure fell with the first beat after the shunt was opened. The fall in systemic arterial systolic pressure for the 42 dogs averaged 52.1 mm. Hg. Aortic diastolic pressure also dropped markedly and immediately, with an average reduction of 45.8 mm. Hg. Although there was either no change or a moderate increase in aortic pulse pressure, it represented a greater proportion of the systolic pressure, so that the mean ratio of pulse to systolic pressure was 0.33 during the control period and 0.57 with the shunt open.

In 8 of the 14 dogs in which it was carefully measured, a systolic gradient developed between the left ventricle and the aorta. The average gradient was 19 mm. Hg. In some animals, however, the left ventricular–aortic gradient was as high as 35 mm. Hg with the shunt open.

Left ventricular end-diastolic pressure increased immediately after the shunt was opened by an average of 9.0 mm. Hg, and the left atrial pressure increased immediately by an average of 4.8 mm. Hg (mean).

Right ventricular and pulmonary arterial systolic pressures increased immediately when the shunt was opened by an average of 8.0 and 8.3 mm. Hg, respectively. Pulmonary arterial diastolic pressure showed a proportionately greater increase (average of 9.9 mm. Hg). Although the actual pulse pressure was thus only slightly reduced, the pulse pressure recorded as percentage of systolic pressure was markedly lowered. In several dogs systolic pressure increased only minimally, whereas the major increase was in the

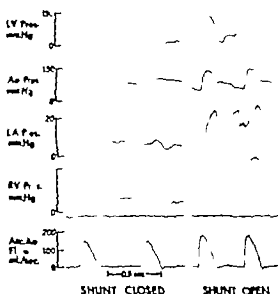


Fig 3 R pr se l pr um a l th t penme f th rt pulm n r h nt LV Left entricle l \ t f l Left trium RV Ri ht entricle Wh th hunt open right v ntricular s t li r urc h be th n ppear wn c deflection f th g l mct r lm t ng

di t lic pressure In 6 dogs a small pressure gradient was produced between the right ventricle and pulmonary artery by constriction of the pulmonary artery at the site of insertion of the shunt This gradient of 6 to 10 mm Hg disappeared when the shunt was opened Right ventricular end diastolic pressure increased immediately and continued to rise slowly over a period of 5 to 10 seconds

The flow of blood in the ascending aorta increased immediately in the beat after opening of the shunt as did left pulmonary arterial and shunt flows The tracings of flow velocity in the brachiocephalic artery and descending aorta showed an immediate decrease in total flow with the development of significant backflow during diastole (This is described in detail below)

These initial responses to opening of the shunt were followed by two general patterns

In 39 of the animals left ventricular and aortic systolic pressures gradually increased over the next minute then stabilized at a new level The left ventricular to aortic systolic gradient increased as the pressure increased (Fig 4) This was associated with a continued slow rise in left atrial mean pressure and a gradual reduction in left ventricular end diastolic pressure which however remained higher than the control level

Right ventricular and pulmonary arterial systolic and pulmonary arterial diastolic pressures continued to increase slowly until a new stable level was reached Right ventricular end diastolic pressure gradually fell from the initial high level to slightly above control

There was an immediate increase in the flow of blood in the ascending aorta followed by a continuing increase up to the period of stabilization The dogs which showed this type of response tolerated the open shunt for the longest period of time and in some animals the pressures and flow remained stable for periods of observation up to 60 minutes

Table I Means and standard deviation of the various pressures during the control period and immediately (up to 5 seconds) after opening of the aortopulmonary shunt

Pressure	Shunt closed	Shunt opened
Left ventricle Systolic	131 4 ± 10 3	115 7 ± 13 7
Left ventricle End diastolic	6 0 ± 3 3	15 0 ± 4 4
Aorta Systolic	129 0 ± 15 1	9(1 ± 1 5
Aorta Diastolic	9(± 11 1	41 0 ± 1 5
Aorta Pulse	42 7 ± 11 7	55 ± 11 8
Right ventricle Systolic	32 8 ± 9 0	40 8 ± 1
Right ventricle End diastolic	1 8 ± 1 1	(0 ± 2 1
Pulmonary artery Systolic	(5 ± (7	31 8 ± 7 (
Pulmonary artery Diastolic	13 8 5 5	21 ± 5 4
Pulmonary artery Pulse	1 5	11 1 ± 3 5
Left atrium Mean	(4 ± 1 1	11 2 4 5

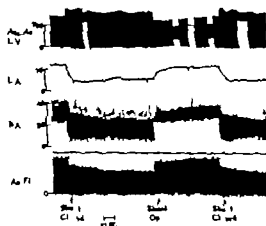


Fig. 4. Example of the first type of response to opening and closure of the aortopulmonary shunt. In the upper tracing aortic and left ventricular pressures were alternately recorded from the same pressure transducer. The second tracing mean left atrial pressure. The lower tracing shows the phasic flow through the ascending aorta. 0 = zero flow level; upward deflections represent forward flow.

Closure of the shunt resulted in an immediate increase in left ventricular and aortic systolic pressures followed by a further rise that lasted from 5 to 15 seconds and then a gradual return to control levels. Left ventricular end-diastolic and left atrial pressures fell precipitously and then more slowly over a period of 5 to 15 seconds. Left ventricular end-systolic pressure increased markedly during the first several beats after closure, then rapidly returned to control. Tracings of blood flow in the ascending aorta indicated a rapid reduction in stroke volume followed by a more gradual decline.

Right ventricular and pulmonary arterial systolic pressures decreased rapidly, then gradually declined further to control levels paralleling the decrease in aortic blood flow. Right ventricular end-diastolic pressure immediately returned to control. In some animals pulmonary arterial systolic pressure fell below control immediately, then gradually re-established a stable control level.

In 4 dogs the aortic, left ventricular systolic and end-diastolic, and left atrial pressures did not change for a variable period (up to 20 minutes) after the initial immediate response. After this period of apparent stability, left atrial and left ventricular end-diastolic pressures increased whereas aortic blood flow and left ventricular systolic pressure decreased. Right ventricular and pulmonary arterial pressures also remained quite stable after the initial immediate changes, then gradually developed a picture characteristic of the second response if the shunt was not closed (vide infra).

The second response (Fig. 5), which was elicited in 13 dogs, has been designated the failure response and was characterized by a continuing decrease in left ventricular and aortic systolic pressures after the immediate fall, a continuing rise in left atrial and left ventricular end-diastolic pressures, and a gradual fall in aortic flow after the initial rapid rise.

Right ventricular and pulmonary arterial systolic pressures, as well as pulmonary arterial diastolic pressure, decreased gradually as aortic blood flow declined. Right ventricular end-diastolic pressure showed a progressive elevation. If the shunt was not closed as these changes proceeded, acute cardiac failure with pulmonary

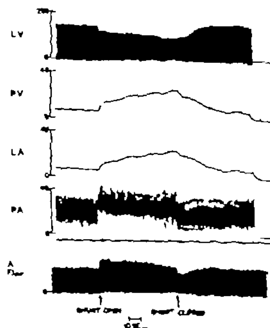


Fig. 5. Example of the second type of response. (Labels: LV, left ventricular; RV, mean pulmonary ...; LA, mean left atrial; and PA, pulmonary arterial pressures recorded. Scale in millimeters of mercury. Lower tracing shows flow in the ascending aorta.

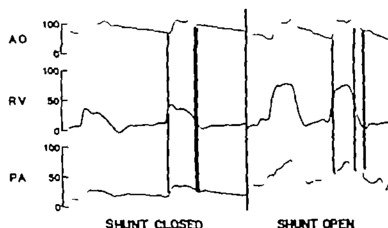


Fig. 6. Aortic, right ventricular and pulmonary arterial pressure tracings with the shunt opened and closed. The first solid line indicates opening of the aortic and pulmonary valves, the second solid line indicates closure of the pulmonary valve, and the broken line indicates closure of the aortic valve.

edema ensued. Fig. 7 shows a failure response in which the shunt was closed too late to prevent death.

In the animal which demonstrated the failure response, closure of the shunt resulted in a slow return of the various parameters to control levels (Fig. 5). Left ventricular and aortic systolic pressures showed only a very small immediate rise followed by a gradual slow rise to levels above control over a period of several minutes depending on the level to which the pressure had previously dropped. The elevated pressure was maintained up to 10 minutes, then slowly returned to control level. Left atrial and left ventricular end-diastolic pressures dropped minimally when the shunt was closed, then slowly returned to control level as left ventricular systolic pressure increased. The flow of blood in the ascending aorta showed a decrease in stroke volume as the shunt was closed, followed by a gradual rise paralleling the increase in left ventricular systolic pressure. Right ventricular and pulmonary arterial systolic and pulmonary diastolic pressures dropped markedly immediately, then gradually increased to control level as aortic flow increased.

Aortic and pulmonary valve opening and closure. Right and left ventricular ejection times were determined by measuring the time intervals between the onset of systolic ejection and the dicrotic notch in the aortic and pulmonary arterial pressure pulses, respectively (Fig. 6). During the control period, right and left ventricular ejection times did not differ markedly; the aortic and pulmonary valves opened almost simultaneously, but closure of the pulmonary valve occurred slightly later than closure of the aortic valve. When the shunt was opened, left ventricular ejection times increased minimally (8 per cent) above the control level. Right ventricular ejection time was markedly decreased (28 per cent). The aortic and pulmonary valves still opened almost simultaneously, but closure of the aortic valve was considerably delayed beyond closure of the pulmonary valve. These findings were confirmed in the two experiments in which the catheter tip pressure transducer was used.

Systemic and pulmonary flows. In the 5 dogs in which cardiac output was measured by the dye-dilution technique, the average control output was 3,100 ml. per minute. When the shunt was opened, pulmonary blood flow increased to an average of 4,900 ml. per minute and systemic flow fell to 2,400 ml. per minute. On the basis of the indicator-dilution curves, the pulmonary to systemic flow ratio averaged 2.1:1. The average total

cardiac output of the right and left ventricles combined was 6,700 ml. per minute with the shunt closed and [illegible],300 ml. per minute when the shunt was open. The volume load was disproportionately placed on the left ventricle with the shunt opened since left ventricular output increased by 58 per cent whereas right ventricular output decreased by 22 per cent.

Oxygen saturations in blood obtained from the pulmonary artery and right ventricle were almost identical when the shunt was closed. Although actual blood flows could not be determined from oxygen saturation data, it was possible to determine pulmonary to systemic flow ratios from the equation

$$\frac{O_2 \text{ sat } LA - O_2 \text{ sat } RV}{O_2 \text{ sat } LA - O_2 \text{ sat } PA}$$

As estimated from the equation, pulmonary-to-systemic flow ratio ranged between 3.5:1 and 6:1, with an average of 4:1.

The oxygen saturation in left atrial and aortic blood was somewhat reduced in all animals in the postoperative period, averaging 86 per cent and ranging from 81 to 90 per cent. When the shunt was opened, there was a consistent increase in saturation of 2 to 4 per cent, with an average saturation of 89 per cent.

Flow contours

1. ASCENDING AORTA. The changes in magnitude of flow in the ascending aorta on opening and closing of the shunt have been described above. The pattern of flow in the ascending aorta during the control period was similar to that described by Kolin[4] and others. After the rapid rise and fall in velocity during systole, a small negative deflection occurred instantaneously with or immediately prior to closure of the aortic valve, followed by a period of zero flow until the next ejection (Fig. 8). There was little change in the flow contour when the shunt was opened. The peak velocity was greater and the total area of the curve increased, which indicated an increase in stroke volume. There was a decrease in the negative deflection at the end of systole in most dogs. The area under the curve increased so that the ratio of areas of the shunt open to those of the shunt closed was an average of 1.6:1, with a variation of 1.3:1 to 1.8:1.

2. DESCENDING AORTA AND BRACHIOCEPHALIC ARTERY. The pattern of flow in these vessels was somewhat different from that in the ascending aorta (Fig. 8). With the shunt closed, the negative deflection at the end of systole was of greater magnitude and duration. When the shunt was open, there was often an initial reduction in the peak velocity, followed by a gradual increase to levels above control as flow in the ascending aorta increased. In addition, there was a marked increase in the negative deflection during diastole, and this negative phase persisted until the onset of the next ejection.

3. LEFT PULMONARY ARTERY. An analysis of the flow tracings from the main pulmonary artery of dogs has been reported by Gur and associates.[7] The patterns of flow in the left pulmonary artery that were obtained in the present study differ from those described for the main pulmonary artery (Fig. 9). In general, there was no negative deflection at the end of systole, and there was a gradual fall in velocity toward zero during diastole. In some instances, zero flow occurred shortly before the next systole, but sometimes the zero flow level was not reached. After the shunt was opened, there was a marked increase in total flow. Peak velocity during systole increased moderately or in some instances not at all. However, the most striking

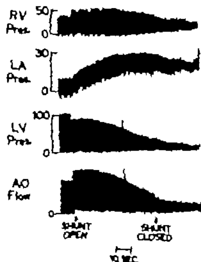


Fig. 7. Failure response with progressive irreversible pulmonary edema.

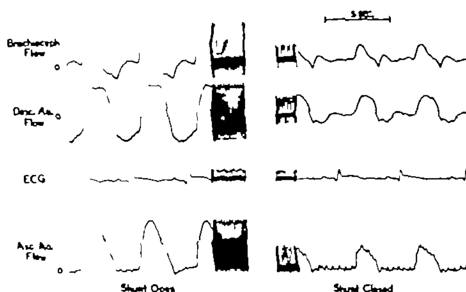


Fig. 3. Flow tracings from transducers around the brachiocephalic artery, descending aorta, and ascending aorta with the shunt open and closed.

changes were a consistent marked increase in diastolic flow velocity and a considerable decrease in the change in velocity from end diastole to peak systole.

4. SHUNT FLOW. Measurement of shunt flow was rather difficult to make, since it was not possible to achieve consistently good contact between the inside of the prosthesis and the flow probes. The contour of the flow tracing when the shunt was opened indicated a continuous flow throughout the cardiac cycle with systolic accentuation (Fig. 10). Peak flow velocity occurred later than the peak flow velocity in the ascending aorta, but at the peak of flow velocity in the descending aorta.

Discussion

The general hemodynamic effects of an aortopulmonary communication are well recognized and are frequently encountered in patients with patent ductus arteriosus. The main features are a marked decrease in the resistance to aortic runoff during systole and diastole, an increased pulmonary blood flow, and an increased volume load on the left side of the heart. The establishment of a large aortopulmonary shunt acutely is not identical with the persistence of a patent ductus arteriosus from birth. A sudden increase in work load is placed on the heart in the experimental animal, whereas in the patient there is a gradual increase in pulmonary blood flow during infancy, usually with adequate time for myocardial compensation by hypertrophy.[4] One instance of the striking contrast is the frequent development of cardiac failure in these animals with relatively small shunts, whereas patients with patent ductus arteriosus may tolerate enormous shunts. In spite of these obvious differences, this preparation has helped in an understanding of the basic hemodynamic mechanisms responsible for some of the clinical features of patent ductus arteriosus.

Right and left ventricular ejection and paradoxical splitting of the second sound. The transmission of aortic pressure to the pulmonary artery in diastole may result in a delayed opening of the pulmonary valve, since the high diastolic pressure in the pulmonary artery makes it necessary for the right ventricle to achieve a higher pressure to open the valve. Similarly, transmission of aortic pressure to the pulmonary artery results in a higher systolic pressure in the pulmonary artery, so that the pulmonary valve closes at a considerably higher pressure and therefore earlier when the shunt is open. The late opening and early closure of the pulmonary valve results in a marked shortening of right ventricular systole

These observations explain the phenomenon of so-called paradoxical splitting of the second sound observed in the patient with a large patent ductus arteriosus. Normally the second sound is split and closure of the pulmonary valve follows closure of the aortic valve by a short interval of 0.04 to 0.06 second. It has been thought generally that the paradoxical splitting of the second sound in which aortic valve closure occurs after pulmonary valve closure is due to prolonged ejection of the left ventricle. The present experiments indicate that in the acutely induced aortopulmonary shunt left ventricular ejection is not significantly prolonged and the primary mechanism responsible for paradoxical splitting is early closure of the pulmonary valve with a shortened right ventricular ejection phase.

Flow contours. The application of electromagnetic flow transducers around the ascending aorta, left pulmonary artery, and descending aorta distal to the shunt permitted analysis of the instantaneous changes in flow as well as changes in flow patterns. The flow tracing from the ascending aorta shows an immediate increase in stroke volume in the first beat after opening of the shunt. This is probably due to the decrease in the aortic outflow resistance and greater emptying of the left ventricle. This has been described by Levy as an alteration of afterload of the ventricle,[9] in which a sudden increase in afterload decreased the stroke volume of the next beat. A similar phenomenon has also been described in association with ectopic beats.[9] The flow tracings from the descending aorta distal to the shunt and

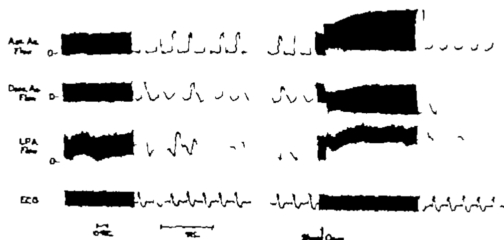


Fig. 9. Flow tracings from transducers around the ascending and descending aorta and the left pulmonary artery.

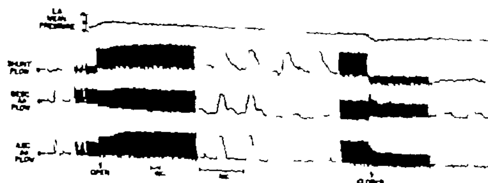


Fig. 10. Flow tracings from transducers around the prosthesis (shunt flow) and descending and ascending aorta.

from the brachiocephalic artery demonstrated a marked increase in the backflow in these vessels in diastole when the shunt was open. This backflow is due to the low resistance to aortic runoff offered by the shunt and pulmonary vascular bed relative to the systemic vascular resistance. This phenomenon explains the angiographic evidence of great fluctuations in forward and backward flow observed in the aorta of patients with aortopulmonary shunts.

The flow contours in the left pulmonary artery showed an interesting but not unexpected pattern. An inconsistent increase in the peak systolic velocity was achieved whereas diastolic velocity was always markedly increased. This indicates that with large aortopulmonary shunts there is a continuing high flow throughout the diastolic phase resulting in a continuous expansion of the pulmonary vessels during the whole cardiac cycle. In other lesions with increased pulmonary blood flow such as atrial and ventricular septal defect a similar increase in diastolic flow in large vessels is not evident and the possibility that this continuous distention of the pulmonary vessels may be particularly important in the production of pulmonary vascular disease has to be considered.

Left ventricular aortic pressure gradients. The mechanism for the systolic pressure gradient which developed between the left ventricle and the ascending aorta when the shunt was opened is not known. It was not observed in all animals and varied from slight (10 mm Hg) to moderate (35 mm Hg). It was not related to constriction by the flow probe around the ascending aorta since it was noted in animals into which a probe had not been inserted. One possible explanation is that it is related to the high stroke volume across a normal aortic outflow. However there was no consistent correlation between the magnitudes of the stroke volume and the pressure gradient which suggests that other factors may be involved. The possibility that forceful contraction of the left ventricle may produce a narrowing of the outflow must also be considered. Similar observations of the systolic pressure gradients have been made in several patients with patent ductus arteriosus and murmurs simulating those of aortic stenosis have been recorded. Both the murmurs and the systolic pressure gradient have disappeared after operation on the ductus alone (personal observation). Morrow and associates[11] have demonstrated this in a patient with an aortopulmonary fenestration in whom a gradient of 63 mm Hg across the left ventricular outflow decreased to 23 mm Hg immediately after the defect was closed.

Methods for estimating shunt size. The inaccuracy of the Fick principle in determining pulmonary blood flow or pulmonary to systemic flow ratios in the presence of a patent ductus arteriosus is notorious and is again demonstrated in the present studies. Pulmonary to systemic flow ratios as estimated from the arteriovenous oxygen differences were consistently considerably higher than those determined by the indicator dilution techniques. The ratio of pulmonary blood flows with the shunt open and closed as determined by indicator dilution curves very closely approximated the results obtained from electromagnetic flowmeter tracings. The Fick method always resulted in an overestimation of pulmonary blood flow because of the high oxygen saturation recorded in the pulmonary artery. This could be related to the fact that during continuous sampling from the major pulmonary arteries blood sampled in the relatively long diastolic phase contains predominantly shunted blood with a high content of oxygen. During systole a better mixed sample that represents shunted blood and mixed venous blood would be obtained but the mean oxygen content over the whole cardiac cycle would be higher than that representing a true mixed pulmonary arterial sample.

Since systemic venous samples obtained from the right atrium or right ventricle are representative of mixed venous blood the systemic blood flow estimated by the Fick method is more accurate than calculations of pulmonary flow.

Arterial oxygen saturation. The increased systemic arterial oxygen saturation which was observed when the shunt was opened is similar to that described by Born and associates.[12] These investigators showed that when the bronchus to a portion of lung was occluded producing inadequate

ventilation systemic arterial saturation was increased when a systemic to pulmonary shunt was established. It was suggested that this was the result of recirculation through the lungs of unsaturated hemoglobin.

In the animals studied postoperatively the recent thoracotomy almost certainly produced some interference with ventilation with perhaps small areas of atelectasis. This was further suggested by the usual occurrence of some decrease in systemic arterial saturation and pO_2 in these animals in the control state. When the shunt was opened respiratory depth and rate increased. It is not certain whether the increased oxygen saturation was due to the recirculation described by Born or whether it was due to an improvement in ventilation associated with opening of the shunt.

Cardiac failure. The factors responsible for the varying responses in different animals have not been elucidated. Many of the animals which manifested the failure response in the immediate postoperative period continued to show similar responses some days after recovery from operation, whereas those animals which tolerated the wide open shunt postoperatively continued to tolerate it later. This suggests that variable losses of blood or variable levels of anesthesia were not responsible for the differing responses. The possible effects of variation in blood volume have been considered since Siegel[19] has suggested that the compensatory response to experimental left to right interventricular shunts in dogs is limited by increasing blood volume. Preliminary observations on the effects of controlled hemorrhage in our animals do not, however, indicate a higher incidence of the failure response after loss of blood but suggest in fact that compensation to opening the shunt may actually be improved under these circumstances.

Although variable levels of light anesthesia with Nembutal in the postoperative period did not seem to alter significantly the response to opening of the shunt in these experiments, other studies (not indicated here) have shown that other general anesthetics can markedly influence the animal's tolerance to the establishment of an aortopulmonary communication.

In general the older animals developed the failure response more readily, whereas healthy young animals tolerated the shunt, which suggests that the ventricles of the young animal are more efficient in handling the sudden increase in volume load.

Summary

A prosthesis made of silicone rubber has been developed for insertion between the aorta and pulmonary artery of dogs. The size of the communication can be controlled in the closed chest unanesthetized animal. The hemodynamic effects of complete acute opening and closing of the shunt have been studied in 35 dogs.

The basic hemodynamic changes are related to a decrease in systemic vascular resistance, an increase in pulmonary blood flow, and direct transmission of aortic pressure to the pulmonary artery. When the shunt is opened there is an immediate decrease in aortic and left ventricular systolic pressure, a rise in pulmonary arterial, left atrial, and left ventricular end diastolic pressure, an increased stroke volume, and an increased heart rate. A systolic gradient between the left ventricle and the aorta frequently develops when the shunt is opened and is probably related to the high stroke volume which occurs.

The pulmonary arterial pressure tracing shows a triphasic contour when the shunt is open; left ventricular ejection is slightly prolonged but the right ventricular ejection period is markedly reduced. This explains the paradoxical splitting of the second sound, which is also observed in some patients with patent ductus arteriosus.

Systemic blood flow is moderately reduced but pulmonary blood flow is increased about twofold. Pulmonary diastolic blood flow is markedly increased so that peripheral pulmonary blood flow becomes much more continuous. During diastole blood flows preferentially into the low resistance shunt and pulmonary vascular system, and a marked backflow during diastole occurs in the descending aorta distal to the shunt.

The animals varied in their ability to tolerate the shunt. After the initial responses some dogs showed a gradual increase in aortic stroke volume and left

ventricular systolic pressure and tolerated the shunt well Others developed a failure response that was characterized by a continuing fall in aortic stroke volume and left ventricular systolic pressure with a rise in left ventricular end diastolic left atrial and pulmonary arterial pressures

We wish to thank Mrs Alice Schmidt for her invaluable technical assistance

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Total anomalous pulmonary venous connection

Electro vectorcardiographic, hemodynamic and anatomic correlations in 11 cases

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Total anomalous pulmonary venous connection refers to that congenital cardiac anomaly in which all pulmonary venous blood eventually drains into the right atrium. An obligatory interatrial communication allows the blood to have access to the left side of the heart.

Numerous reviews have emphasized the clinical diagnosis,[1-3] pathologic evaluation,[4-8] and techniques of surgical repair.[9-11] However, comparatively little on this clinical entity has been written specifically concerning the electrocardiogram[1,12] and no studies describing the vectorcardiogram nor the relation of the electrocardiogram and vectorcardiogram to hemodynamic data have appeared. We have seen 11 patients with total anomalous pulmonary venous connection unassociated with any other cardiovascular anomaly, and it is the purpose of this report to analyze these cases, emphasizing the electro vectorcardiographic findings and their correlation with hemodynamic measurements and anatomic data.

Case material and methods

All 11 patients (Table I) were evaluated at the University of Florida Teaching Hospital. The diagnosis was established by autopsy in 8 cases, by surgery in 2 (Cases 6 and 10), and by cardiac catheterization in one (Case 11).

The sex ratio of 1:1 conforms to previous reports.[4-7] Four patients were born at premature weights. All the patients were born during a 7 month period of the year, February to August inclusive. The actual dates of conception could not be ascertained.

All 9 operations were attempts at complete repair. Seven patients, all under 1 year of age, died in the immediate postoperative period, whereas in Cases 6 and 10 repair was successful.

Five of the cases were of the coronary sinus connection type, an unusually high incidence, since in previously reported cases anomalous connection of the pulmonary veins to the left superior vena cava was the most common type.

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Table I. Historical and pathologic data in 11 cases of total anomalous pulmonary venous connection

Case number	Birth (mo./yr.)	Birth weight (grams)	Sex	Age at catheterization (mo.)	Site of APVC	Age at operation (mo.)	Average thickness of right ventricular wall (mm.)	Average thickness of left ventricular wall (mm.)
1	July 1961	2 390	F	2	LSVC	4*	4 75	6 0
2	June 1961	2 770	F	6	LSVC	7	7 25	7 75
3	May 1962	3 520	M	2	LSVC	2	6 50	4 75
4	May 1960	3 400	M	?	CS	5	9 0	8 25
5	February 1962	3 960	M	?	RA	7	12 0	6 5
6	February 1945	2 460	M	17 yr.	RA	17 yr.	—	—
7	August 1960	2 80	F	5	CS	5	6 0	7 0
8	May 1960	2 180	F	5	CS	Not operated†	8 25	6 25
9	July 1959	3 170	F	10	CS	12	7 0	8 0
10	March 1961	3 740	M	13	CS	21	—	—
11	June 1962	2 380	F	7	LSVC	Not operated	—	—

*[illegible] of two independent [illegible] [illegible] described [illegible] text.
†Died at the age of 8½ months.
APVC: Anomalous pulmonary [illegible] connection. LSVC: Left superior [illegible]. CS: Coronary sinus. RA: Right atrium.

Table II. Catheterization data in 11 cases of total anomalous pulmonary venous connection

Case number	Right atrial pressure (mm. Hg)	Right ventricular pressure (mm. Hg)	Systemic arterial pressure (mm. Hg)	Pulmonary arterial pressure (mm. Hg)	Per cent oxygen saturation of right heart	Per cent oxygen saturation of systemic artery
1	9/5	40/2 ———	92/55	NE	86 ——— RA	75
2	12/	NE	94/56	NE	83 RA	74
3	22/5	135/0 to 15 ———	85/43	NL	74 RV	58
4	18/–5	105/0 to 10	90†	NE	80 RV	72
5	18/8	60/3 ———	92/58	NE	86 ——— RV	8
6	5/1	42/ 2 to 5 ———	114/70	33/17	91 ——— RA	85
7	10/0	30/0 to 6	110†	44/14	88 ——— PA	82
8	18/0	95/0 to 9	0†	87/43	56	60
9	2	67/8 ———	71/39	67/48	96 ——— LA	86
10	/0	4 /4 ———	85/60	NE	96 ——— RV	97
11	/3	50/2 9 ———	90/50	42 10	77 ——— PA	77

———— Connects simultaneously obtained values.
†Clinically obtained by flush technique.
NE: Not entered. RA: Right atrium. RV: Right ventricle. PA: Pulmonary artery.

Right ventricular wall thickness (Table I) was determined from the average of two values measured 0.5 cm below the tricuspid valve and 1 cm below the pulmonic valve. Left ventricular wall thickness was determined from the average of two values measured 1 cm below the mitral valve but above the posterior papillary muscle and 1 cm below the aortic valve.

All electrocardiograms were taken on a Sanborn instrument. Fourteen leads, the six standard leads and Precordial Leads V_{4R} to V_7, were obtained on all patients. The vectorcardiograms were taken using the *Grishman cube system. Horizontal,* right sagittal, and frontal views were recorded on a Sanborn vectorcardiograph. Photographs of the oscilloscopic patterns were made with a Dumont Polaroid camera, with the electron beam interrupted every 2.5 milliseconds.

Catheterization of the right side of the heart was performed on all patients using parenteral sedation with no general anesthesia. A venous catheter was introduced into a saphenous vein in all patients except Case 6, in whom the median basilic vein was used. In 8 cases a No. 20 polyethylene or nylon catheter was introduced into either the brachial or femoral artery. In the other 3 cases an arterial sample was drawn by puncture of a femoral artery. The advantage of an indwelling arterial catheter, as indicated in Table II, is that simultaneous arterial and right heart oxygen saturations and pressures could be obtained. Arterial and venous pressures were measured using Statham strain gauges with the reference zero set at the mid chest level. Oxygen saturations were determined with a Waters cuvette oximeter model No. XC 50B and an Emsco oximeter amplifier. Galvanometer deflections were recorded on a Minneapolis Honeywell No. 1108 Visicorder and were calibrated against a Beckman DU spectrophotometer. Pulmonary and systemic blood flows were calculated on the basis of the Fick method. When samples of blood from the pulmonary artery were not obtained, samples from the right ventricle were used for this calcula-

Table III Electrocardiographic data in 11 cases of total anomalous pulmonary venous connection

Case number	Age at time of ECG (yr.)	Tallest P (mm.) and lead	P-R interval Lead II	Frontal plane mean QRS axis (degrees)	QRS pattern and deflection (mm.)		
					[illegible]	[illegible]	[illegible]
1	2	3 5 II	0 11	+110	rSR 1/8 3/5	R 14	qRS 2/18 5/9
2	4	2 0 II	0 12	+150	QR 4/8	rR 0 5/22 5	qRS 5/3 5/16
3	5	4 5 V	0 14	+130	qR 0 5/4 0	Rs 23/3	rS 2 0/14
4	2/3	4 0 V	0 12	+120	QR 4/5	qR 1 3/11 3	RS 8/16
5	1	3 5 V	0 15	+1 0	rSR 5/3 5/10 5	R 1 5/23	qRS 1 5/6 /10 5
6	17 r	4 0 V	0 21	+9	QS 4 3	rSR 5/ /4 5 1 5	RS 19 5/11
7	5	3 0 V	0 11	+95	rSR 3/6/5 5	rsR 5/ 5 14	qRS 3/9 5/9
8	[illegible]	3 0 II	0 12	+95	QR 12 5/8 5	qR 1/21	RS 1 /23
9	[illegible]	4 0 II	0 10	+9	[illegible] 3 1	[illegible] 13 5	qRS 5/5 5/[illegible]
10	13	3 0 II	0 12	+160	QR 3/6	RS 19/7	RS 4/8 5
11		3 0 V	0 15	~90	QR 2 7	qR 2 5/6	RS 25/18

[illegible] ECG [illegible] Lead II

tion. These are considered to be satisfactory since multiple samples from several sites in the right ventricle had essentially identical oxygen contents.

Discussion of electrocardiographic findings

The electrocardiographic findings are summarized in Table III. Certain features should be emphasized.

All 11 electrocardiograms showed a peaked P wave characteristic of right atrial enlargement either in Lead II or Lead V or V_1. The frontal plane mean QRS axis was greater than 90 degrees in all except Case 11. This patient demonstrated a frontal plane pattern characteristic of endocardial cushion defects, that is, a superior and leftward orientation of the QRS loop producing an axis of

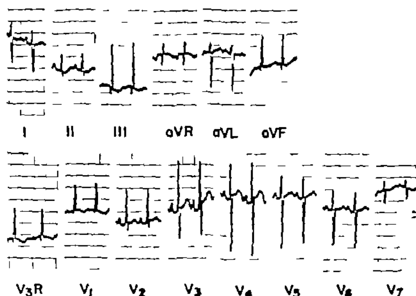


Fig. 1. Electrocardiogram of a 20-d?? old male infant with total anomalous pulmonary venous return to the coronary sinus. Note the q wave in Lead V and the tall peaked P wave in Lead V.

Table IV. Electrocardiographic, hemodynamic, and pathologic correlations in 10 cases of total anomalous pulmonary venous connection

Case number	Site of TAPVC	Right ventricular systolic pressure / Systemic arterial systolic pressure	Pulmonary flow / Systemic flow	Right ventricular / Left ventricular wall thickness	Precordial q wave	Ratio R/S in Lead V_1	Mean QRS axis in frontal plane (degree)	Height of R wave in Lead aV_R (mm.)
6	RA	0.37	5.6	—	None	1.8	+95	0
1	LSVC	0.43	2.5	0.8	N	2.1	+110	5.0
	CS	0.45	4.5	0.85	N	1.1	+95	5.5
10	CS	0.50	2.6	—	N	0.5	+160	6.0
11	LSVC	0.52	2.2	—	N	1.6	−50	7.0
5	RA	0.65	1	1.8	N	0.6	+170	10.5
9	CS	0.94	2.6	0.9	N	0.8	+95	1.0
4	CS	1.2	1	1.1	N	0.5	+120	5.0
8	CS	1.3	—	1.3	N	0.8	+95	8.5
3	LSVC	1.6	0.?	1.4	N?	0.1	+130	4.0

TAPVC, total anomalous pulmonary venous connection; LSVC, left superior vena cava; CS, coronary sinus; RA, right atrium.

−50 degrees Since operative and necropsy data are not available it is not known whether an endocardial cushion defect (e g an ostium primum defect as the interatrial communication) exists Right axis deviation is a consistent finding in all previously published cases except for Case 3 of Marini and Bauersfeld [1] and one case of Morales and co workers [11] Both of these cases also demonstrated marked left axis deviation with a mean frontal plane QRS axis of −90 degrees Again it is not known whether endocardial cushion defects were in fact present

A q wave was recorded in the right precordial leads in only 3 cases and in the left precordial leads in 6 cases The electrocardiographic diagnosis of right ventricular hypertrophy was made in all 11 patients None showed electrocardiographic evidence of left ventricular hypertrophy

Marini and Bauersfeld[1] reported on the electrocardiograms in 11 cases of total anomalous pulmonary venous connection In 4 of their cases there was a right precordial q wave and in 1 a left precordial q wave These authors made the observation that the ratio P/P R (P = duration of the P wave and P R = duration from the end of P to the peak of the R wave in Lead II) was 1 0 or less in all their cases whereas normal values ranged form 0 95 to 1 3 Although not tabulated we made this calculation and found that in 4 of our cases the ratio was 1 0 or greater with a range of 0 5 to 1 3 and the average value for the entire group was 0 87 Thus our findings do not support the value of utilizing this ratio on the electrocardiographic diagnosis of right atrial enlargement

Keith and co workers[3] initially suggested

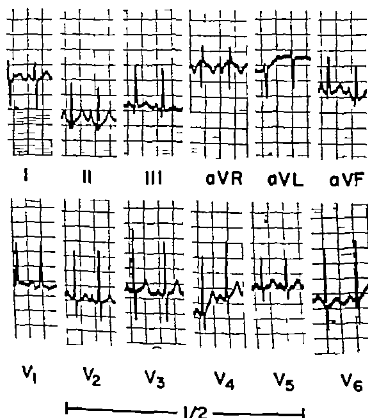


Fig 2 Electrocardiogram of 2 month-old female infant with total anomalous pulmonary venous return to the left superior vena cava Note the presence of 2 0-mm q wave in Lead V in the face of right ventricular hypertrophy A tall peaked P wave is seen in Lead II

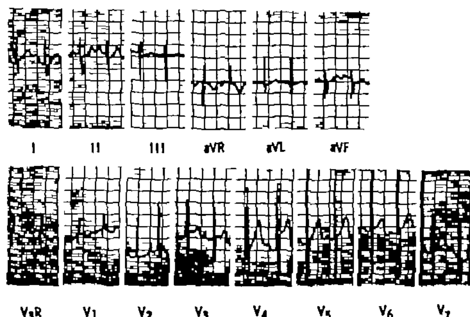


Fig 3 Electrocardiogram of a 7 month old female infant with total anomalous pulmonary venous return to the left superior vena cava Note the predominant negativity in Lead II III and aV A qR pattern is present in Lead V_{3R} and V

the diagnostic importance of a right precordial q wave in this disease since they observed a q wave in either Precordial Lead V_{3R} or V_1 in 8 of 9 cases Six of these 8 cases were of the left superior vena cava type Keith and associates also observed tall peaked P waves in 7 of their 9 cases

Guntheroth and co workers[4] reported a right precordial q wave in 5 of 20 cases and suggested that even in these 5 the pattern actually may have been an rsR with an isoelectric r Tall peaked P waves were seen in 13 of their 20 cases

Morales and associates[13] reported on 8 patients with total anomalous pulmonary venous drainage who ranged in age from 18 months to 28 years only one of whom demonstrated a q wave in Lead V_1

If these five groups including our own are summed the total incidence of a right precordial q wave is 21 of 59 (36 per cent)

Right atrial enlargement and right ventricular hypertrophy were indicated by all electrocardiograms in our cases Right axis deviation was present in all except Case 11 There were significant differences despite this conformity between the electrocardiograms demonstrating the variability present among this group The usual electrocardiographic findings as well as some of the more important differences are illustrated in Figs 1 3 The electrocardiogram of Case 4 (Fig 1) demonstrates a q wave in Lead V_1 and a tall peaked P wave in Lead V_1 The electrocardiogram of Case 1 (Fig 2) shows the presence of a significant q wave in Lead V_1 with an abnormal P wave being evident in Lead II The q wave in Lead V_1 which was recorded in this patient at the age 2 months was present in the face of marked right ventricular hypertrophy This finding was also present in Cases 5 7 and 9 The electrocardiogram of Case 11 (Fig 3) illustrates the standard and augmented limb lead pattern usually seen in endocardial cushion defects with predominant negativity of the QRS complex in Leads II III and aV_F Right ventricular hypertrophy is evidenced by the qR pattern in Precordial Lead V_1 and the characteristic P waves are seen in Lead V

The vectorcardiogram

Vectorcardiograms were obtained on all patients except Case 8 and are reproduced in Fig 4 All 10 vectorcardiograms were diagnostic of right ventricular hypertrophy The horizontal and frontal plane QRS loops were all inscribed clockwise except

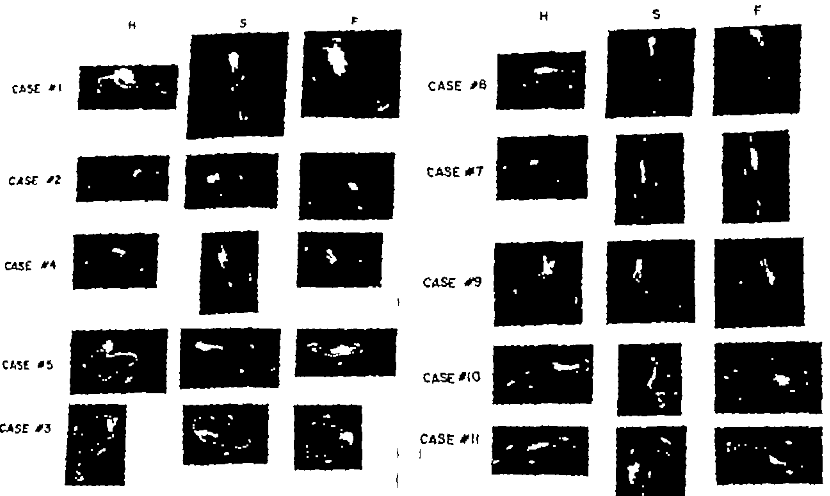


Fig 4 Vectorcardiogram (Frank lead system) in 10 cases of total anomalous pulmonary venous return

for the frontal plane QRS loop in Case 11. This case demonstrated the superiorly oriented counterclockwise loop that is commonly seen in endocardial cushion defects. Six vectorcardiograms show counterclockwise inscription in the right sagittal plane, one was inscribed as a figure of eight, and 3 were inscribed clockwise. The anterior and rightward shift of the QRS loop was evident in all cases.

The vectorcardiogram gives assistance in determining whether the initial QRS force in Lead V_{3R} or Lead V_1 produces a small q wave or actually an isoelectric r in an rsR complex as suggested by Guntheroth and co-workers.[4] As can be seen in the vectorcardiograms of Cases 4 and 11, the initial portion of the horizontal loop is directed to the left and on the anterior-posterior dividing line, thus recording as an initial negative deflection (q wave) as viewed from Lead V_1. Of the other 8 vectorcardiograms, the initial QRS force in the horizontal plane is directed to the right in 6 cases, and thus would be expected to produce a q wave in Lead V_6 or V and not in Lead V. This expected finding was noted in all 6 cases. In the other vectorcardiograms (Cases 3 and 6) the initial QRS force is directed to the left but sufficiently anterior so as not to inscribe a q wave in any of the standard precordial leads (V_{3R} to V).

Cardiac catheterization

Table II contains the pertinent catheterization data. In each instance, except Case 8, the oxygen saturation of the right heart equaled or exceeded the peripheral arterial saturation. The diagnostic importance of this point has been emphasized previously.[4]

Right ventricular pressure was elevated whenever it was measured. The elevation of right atrial pressure probably reflects the fact that many of the patients were in congestive failure at the time of catheterization of the right side of the heart.

Correlations

In Table IV the 10 cases in which satisfactory hemodynamic data are available have been arranged in ascending order of the value of the following ratio: right ventricular systolic pressure/systemic arterial systolic pressure. In 3 cases (Cases 4, 7, 8) only flush blood pressures are available. It is recognized that this value perhaps correlates better with mean arterial pressure than with systolic arterial pressure. In order to allow ease of correlation, information obtainable from Tables I-III has been added.

Although certainly not conclusive, certain trends are suggested. The higher pressure ratio appears to be associated with a lower pulmonary/systemic flow ratio, the presence of a q wave in Precordial Lead V_1, and a lower R/S wave ratio in Lead V_6. These latter electrocardiographic complexes probably indicate a greater degree of right ventricular hypertrophy. The right ventricular/left ventricular wall thickness ratios correlate directly with the right ventricular/left ventricular systolic pressure ratios. The higher wall thickness ratios occurred consistently in the cases with the highest pressure ratio except for Case 5. At autopsy in Case 5 extensive old patchy infarcts of the right ventricle were found involving mainly the anterior wall and outflow tract. This probably accounts for much of the unexpected thickness of the walls of this chamber. Furthermore, in Case 5 autopsy was performed 5 months after cardiac catheterization, and thus significant changes in pressure may have occurred in the interim.

The mean QRS axis in the frontal plane and the height of the R wave in Lead aV_R show no consistent relationship to the other measurements in this table.

Conclusions

Although we recognize that the accumulation of similar data is needed, the following conclusions may be drawn from the information presented.

1. The mean QRS axis in the frontal plane is usually greater than +90 degrees and the QRS forces in the frontal and horizontal planes of the vectorcardiogram are consistently inscribed in a clockwise direction, except for the occasional case in which there is marked leftward and superior orientation of the QRS forces.

2. The presence of a right precordial q wave in the electrocardiogram and vectorcardiogram is uncommon in our series

The vectorcardiogram is of invaluable assistance in determining whether a q wave or an isoelectric r wave comprises the initial portion of the QRS complex in the right precordial leads. In any case the absence of a right precordial q wave is not evidence against the diagnosis of total anomalous pulmonary venous connection.

3. Tall peaked P waves, indicating right atrial enlargement, are usually seen in either Lead II or Precordial Lead V or V.

4. The specific type of total anomalous pulmonary venous connection cannot be diagnosed by the degree of right ventricular hypertrophy recorded on the electrocardiogram and vectorcardiogram.

5. Patients with higher right ventricular left ventricular pressure ratios and lower pulmonary systemic blood flow ratios appear to have more severe right ventricular hypertrophy by pathologic criteria.

6. The vectorcardiogram suggests that lower right ventricular left ventricular pressure ratios and higher pulmonary systemic flow ratios are usually associated with more leftward and anterior QRS forces, whereas in cases of higher pressure ratios and lower flow ratios the QRS forces show a more rightward and anterior shift.

7. The presence of a right precordial q wave suggests that the systolic pressure in the right ventricle may be at systemic levels.

Summary

An analysis of 11 cases of total anomalous pulmonary venous connection indicates that the electro-vectorcardiogram consistently shows right axis deviation, right ventricular hypertrophy, and right atrial hypertrophy. The degree of elevation of right ventricular pressure may be correlated with certain electro-vectorcardiographic, hemodynamic, and anatomic observations.

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The use of amyl nitrite in the hemodynamic assessment of aortic valvular and muscular subaortic stenosis

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The demonstration of a pressure gradient between the left ventricle and the aorta is necessary for the hemodynamic verification of aortic stenosis. In mild fixed-orifice stenosis the diagnosis may remain unconfirmed because of the absence of a significant gradient at rest. Although exercise can be used to induce a diagnostic difference in ventriculo-aortic systolic pressure, the currently used technique of percutaneous transseptal catheterization of the left side of the heart makes leg exercise cumbersome. In muscular subaortic stenosis the gradient may vary spontaneously, so that evidence of obstruction may not be present at the time the pressures are recorded.[1] Exercise may induce a diagnostic gradient, but it is employed with the same limitations as in fixed-orifice aortic stenosis. In muscular subaortic stenosis, increased obstruction to left ventricular outflow can be induced by premature beats,[2] by the Valsalva maneuver,[3] or by the pharmacologic effects of isoproterenol[1,4] or digitalis.[2] These methods, by permitting the definitive recognition of muscular subaortic stenosis in patients with little or no resting gradients, have been important in the clinical and hemodynamic study of this type of outflow obstruction. The purpose of this report is to describe the use of amyl nitrite inhalation as a safe, convenient, and reproducible means of accentuating the gradient in both fixed-orifice aortic stenosis and muscular subaortic stenosis.

Methods

The patients were studied in the cardiovascular laboratories of the Georgetown University Hospital or the District of Columbia General Hospital. Catheterization of the left side of the heart was performed by the retrograde femoral technique[5] or by the transseptal technique.[6] Left ventricular and brachial arterial pressures were inscribed simultaneously on either an Electronics for Medicine re-

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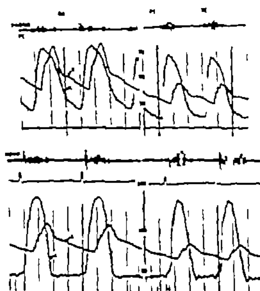


Fig. 1. Representative tracings from 2 patients with valvular aortic stenosis. Simultaneously recorded left ventricular and brachial arterial pressures prior to and during peak effect of amyl nitrite demonstrate a gradient only after inhalation of amyl nitrite by S. T. (*upper section*) and illustrate the accentuation of the existing gradient in Patient N. M. (*lower section*). Note the increase in the intensity of the systolic murmur after the nitrite effect in both instances. Paper speed of 75 mm. per second.

corder or on a Sanborn No. 550M polybeam recorder. The P23Db Statham or Sanborn strain gauges were calibrated to respond identically. Systemic cardiac output at rest was determined in duplicate by the indicator dilution technique using Cardiogreen dye. Dye was injected into the pulmonary artery or into the left ventricle and blood was withdrawn from the brachial artery.

Amyl nitrite was inhaled from a broken phial held lightly over the nose with a small cloth.[19] When the phial was broken attention was directed to the distinct "pop" that indicated fresh, potent drug. The subject was instructed to increase the rate and depth of respiration only slightly but was specifically told not to hyperventilate. In order to minimize apprehension the patient was warned of the sensation of cutaneous flushing and tachycardia that often followed the inhalation of amyl nitrite. The duration of inhalation (generally 10 to 20 seconds) was based upon the response of the monitored systemic arterial pressure. Inhalation was stopped when the brachial systolic pressure fell by 25 to 35 mm. Hg. The pressure then continued to decline moderately before reaching a fairly stable trough. The foregoing method of administration permits amyl nitrite to be used safely. However, prolonged inhalation can cause excessive declines in arterial blood pressure, a response to be avoided especially in patients with aortic stenosis.

Four patients with aortic valvular stenosis and 4 patients with muscular subaortic stenosis were studied (see Table I for clinical features). The data in one patient (A. H.) with muscular subaortic stenosis have been reported elsewhere. In the patients with valvular aortic stenosis phonocardiograms recorded typical crescendo-decrescendo (ejection) systolic murmurs which were loudest in the second right intercostal space, which radiated into the neck, and which characteristically increased after the inhalation of amyl

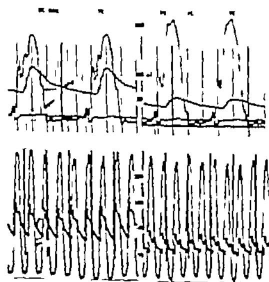


Fig. 2. Pressures recorded simultaneously from the left ventricle and the brachial artery in patients with muscular subaortic stenosis. The administration of amyl nitrite increased the gradient in both patients. Note the accentuation of the double-peaked brachial arterial tracing after amyl nitrite in Patient E. T. (*lower section*). Upper tracings recorded at paper speed of 75 mm. per second. Lower tracings recorded at paper speed of 25 mm. per second.

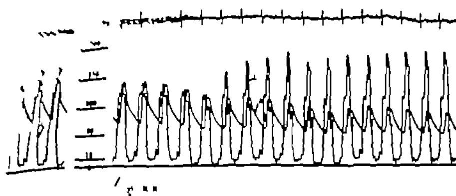


Fig. 3 Patient V. H. with muscular subaortic stenosis and no gradient in the control tracing. Amyl nitrite induced a peak LV–BA systolic gradient of 100 mm. Hg. Observe the initial parallel fall in both left ventricular (LV) and brachial arterial (BA) pressure with subsequent divergence. See text for explanation. Paper speed of 25 mm. per second.

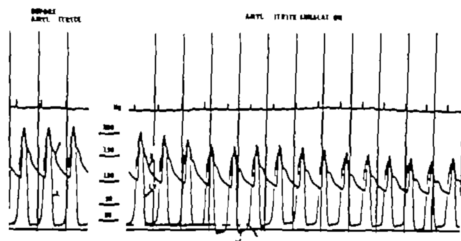


Fig. 4 The effect of inhalation of amyl nitrite in a patient with left ventricular hypertrophy due to essential hypertension. The oblique arrow at the end of the marker indicates the end of 20 seconds of continuous inhalation of the drug. The left ventricular and brachial arterial systolic pressures do not diverge but instead fall in parallel. Paper speed of 25 mm. per second.

nitrite (Fig. 1). Hemodynamic verification was based upon the detection of an aortic gradient in excess of 15 mm. Hg either in the control tracings or after the inhalation of amyl nitrite. In the patients with muscular subaortic stenosis the phonocardiograms also recorded typical ejection systolic murmurs which increased after inhalation of nitrite, but these murmurs were loudest at the apex and radiated poorly, if at all, into the neck. Aortic ejection sounds or murmurs of aortic insufficiency were neither heard nor recorded. The arterial pulses were brisk. Poststenotic dilatation was absent except in Patient M. B. This type of dilatation of the ascending aorta was a unique observation in muscular subaortic stenosis and is to be reported in detail separately.[7] Hemodynamic verification of obstruction to left ventricular

outflow was based upon the detection of a gradient in excess of 15 mm Hg either in the control tracings or after the administration of amyl nitrite or Isuprel.[6] Justification for classifying this obstruction to outflow as muscular subaortic stenosis was based upon the criteria of Brockenbrough and associates.[7] Each patient in this group had a diagnostic decline in the post premature beat brachial arterial pulse pressure.[8] In one patient (A. H.) the diagnosis was further verified by left ventricular angiocardiography.

Results

The results are summarized in Table II. Amyl nitrite consistently increased the left ventriculo-brachial arterial systolic gradients in both fixed-orifice aortic stenosis and muscular subaortic stenosis (Fig. 1-3). The separation of the systolic pressures was achieved primarily by disproportionate decline in brachial arterial pressure. In 5 patients the left ventricular systolic pressure declined or remained unchanged. In 3 instances, however, the left ventricular systolic pressure actually rose. The normal response to amyl nitrite inhalation is illustrated in Figure 4. Left ventricular and brachial arterial systolic pressures do not separate but instead fall in parallel. In 2 patients with valvular aortic stenosis and in 2 patients with muscular subaortic stenosis, nitrite inhalation detected the presence of outflow obstruction not otherwise apparent since the control systolic gradients were absent or trivial.

Discussion

The inhalation of amyl nitrite causes a decrease in peripheral vascular resistance with a subsequent decline in systemic arterial pressure.[10,11] These effects always precede the acceleration of cardiac rate which is reflex tachycardia. When systemic flow is measured at the height of the amyl nitrite effect, there is a marked *rise* in cardiac output which is attributable to the increase in heart rate, since stroke volume is essentially unaltered. The velocity of ejection probably increases because the duration of systole shortens, *even* though stroke volume remains unchanged.[14]

Table I. Summary of physical findings and electrocardiographic and chest roentgenographic data in patients studied

Patient	Carotid thrill	Carotid pulse rate of rise	Maximum intensity of systolic murmur	Systolic ejection click	Aortic diastolic murmur	ECG	Poststenotic dilatation	Aortic valve calcification
Valvular aortic stenosis								
S. T.	+	Slow	2nd Right intercostal space	No	Yes	LVH†	Y	N
L. D.	+	Moderately low	2nd Right intercostal space	Ye	Yes	Normal	Y	N
S. Z.	+	Normal	2nd Right intercostal space	Yes	No	LVH	Ye	N
N. M.	+	Slightly decreased	2nd Right intercostal space	N	Yes	LVH	Y	Y
Muscular subaortic stenosis								
H. M.	0	Brisk	Apex	N	No	LVH	N	No
A. H.	0	Brisk	Apex	No	No	RBBB‡		N
M. B.	0	Brisk	Apex	No	No	LVH	No	No
F. T.	0	Brisk	Apex	No	No	LVH	No	No

Th[illegible] [illegible] superimposed [illegible] hypertrophy [illegible] [illegible] in the [illegible]
‡Right bundle branch block.

Table II. Hemodynamic data before and during peak effect of amyl nitrite

Patient	At rest				After inhalation of amyl nitrite			Hemodynamic effect due to amyl nitrite		
	LV pressure (mm Hg)	BA pressure (mm Hg)	Peak LV-BA systolic gradient (mm Hg)	Cardiac index (L/min/M²)	LV pressure (mm Hg)	BA pressure (mm Hg)	Peak LV-BA systolic gradient (mm Hg)	Change in LV pressure syst/diast (mm Hg)	Decrease in BA pressure syst/diast (mm Hg)	Increase in LV-BA systolic gradient (mm Hg)
Valvular aortic stenosis										
S. T.	164/36	166/78	0	2.1	148/20	90/50	58	−16/−16	76/28	58
I. D.	118/10	104/66	14	2.7	100/2	68/42	37	−18/−8	36/24	18
S. Z.	174/9	139/79	35	2.8	270/7	96/44	134	+46/−1	53/35	99
N. M.	170/16	114/58	56	2.4	166/20	76/46	90	−4/+4	38/12	34
Muscular subaortic stenosis										
H. M.	125/17	125/70	0	2.8	119/10	79/50	40	−6/−7	46/20	40
V. H.	170/10	160/90	10	2.0	180/10	90/50	90	+10/0	70/40	80
M. B.	174/16	110/58	64	2.2	206/16	59/38	148	+32/0	52/20	66
I. T.	240/10	140/85	100	3.4	240/10	90/60	150	0/0	50/25	50

LV = left ventricular; BA = brachial artery.

An increase in venous return is believed to be associated with the rise in cardiac output since the magnitude of the augmentation in flow is too great to be derived solely from the thoracic reservoir[11] Increased venous return after the inhalation of amyl nitrite is further supported by a decrease in mean recirculation time[10] which would be unlikely if significant venous pooling occurred Evidence that the increased venous return is reflected in events on the left side is suggested by the rise in left atrial pressure after the inhalation of amyl nitrite in patients with mitral stenosis[14] In aortic stenosis augmentation of the gradient may relate to the increase in magnitude and rate of flow across the aortic orifice as well as to the decline in systemic arterial pressure[10] In the absence of obstruction to outflow left ventricular and aortic systolic pressures decline in parallel after the administration of amyl nitrite (Fig 4) In the presence of aortic stenosis however systemic pressure drops considerably but left ventricular systolic pressure cannot fall in parallel (Figs 1 and 2) Amyl nitrite induces similar directional changes in the height of the brachial arterial and left ventricular pulses in both fixed orifice stenosis and muscular subaortic stenosis However in 2 of the 4 patients with muscular subaortic stenosis (A H M B) there was initially a parallel fall in both left ventricular and brachial arterial pressures (Fig 3) The brachial pressures then *continued to decline while the left ventricular* pressures returned to control levels or higher Because the degree of obstruction is not fixed in muscular subaortic stenosis the aortic and left ventricular pressures may initially fall proportionately in response to the decline in systemic resistance induced by the inhalation of amyl nitrite Should amyl nitrite then cause a decrease in left ventricular systolic size analogous to the decrease caused by nitroglycerin[16] the outflow tract may be narrowed and the gradient may accordingly be increased The Valsalva maneuver by reducing ventricular filling also causes a decrease in left ventricular systolic size[15] and also results in an increase in the degree of obstruction[11] The concept that a decline in left ventricular end systolic size relates to the magnitude of the gradient in muscular subaortic stenosis is supported by observations that a decrease in systolic size occurs with drugs or maneuvers which augment obstruction to left ventricular outflow[17, 8] Furthermore methoxamine a sympathomimetic agent with negligible inotropic effect and little effect on cardiac output or heart rate causes an increase in end systolic size and a decrease in left ventriculo aortic gradient in muscular subaortic stenosis[8, 1]

The problem of hemodynamic documentation of mild fixed orifice aortic stenosis has been alluded to Hancock and associates called attention to the absence of gradients in mild aortic obstruction Two of our patients (S T and L D) with convincing clinical evidence of valvular aortic stenosis had either trivial or no resting gradients Amyl nitrite by inducing substantial gradients (Table II) established the diagnosis in each case Muscular subaortic stenosis may also occur with little or no difference in left ventriculo aortic systolic pressure In 2 patients in this category (H M and A H) amyl nitrite contributed to the diagnosis by inducing a diagnostic gradient (Table II) Since amyl nitrite accentuates the gradient in valvular aortic stenosis as well as in muscular subaortic stenosis it cannot necessarily be used to distinguish one from the other However the diagnosis of muscular subaortic stenosis is suggested if the inhalation of amyl nitrite changes the shape of the arterial pulse to the characteristic double peaked contour (Fig 2) Amyl nitrite may prove to be safer than isoproterenol in the diagnostic assessment of aortic stenosis since ventricular irritability or coronary insufficiency can be aggravated by the latter drug but not by the former

Summary

The hemodynamic effects of amyl nitrite were studied in 4 patients with valvular aortic stenosis and in 4 patients with muscular subaortic stenosis In all 8 subjects amyl nitrite significantly increased the left ventriculo aortic gradients Two patients in each group had nondiagnostic gradients in control tracings but had

diagnostic postinhalation gradients These observations indicate that the inhalation of amyl nitrite is a safe convenient and reproducible means of accentuating the gradient in both fixed orifice aortic stenosis and muscular subaortic stenosis Mechanisms relating to the development of increased obstruction of the outflow tract are believed to differ in the two groups

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Addendum

Since this paper was submitted a report has appeared which is in agreement with our findings that amyl nitrite accentuates the systolic gradient in muscular subaortic stenosis [22]

A single observation suggests that amyl nitrite may be the most sensitive agent available to induce obstruction to outflow in the case of muscular subaortic stenosis [4] A patient with this condition who did not exhibit a systolic gradient at rest inhaled amyl nitrite and a systolic gradient of 58 mm Hg became manifest Neither infusion of isoproterenol at a concentration of 4 µg per milliliter nor the Valsalva maneuver succeeded in evoking evidence of obstruction

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Studies in cerebral circulation
Methods for the stereoscopic demonstration of the human cerebral microcirculation
Preliminary observations on the arterial supply of the red nucleus

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Those interested in the study of the microcirculation are faced with the perplexing problem of visualizing three-dimensional arrangements of component blood vessels. Many methods have been devised to demonstrate important vascular interrelationships. Some have been accepted through time-honored usage and, although accurate, are limited in application. The use of stereoscopic photographic pairs are invaluable for survey or analytical purposes but are cumbersome and inadequate when used to illustrate material presented to a group of observers. A better method is needed for the illustration of appropriate three-dimensional photographic information. The purpose of this paper is to describe a method which has been devised for the production of polarizing lantern slide stereographs that can be projected and viewed by an audience using conventional photographic techniques and ordinary projection equipment.

Materials and methods

The methods described are applicable for the production of any size of lantern slide or transparency, including the 2 by 2 inch size. In general, halftone black and white stereophotographic pairs are used. Proper contrast is critical in the format so that negatives of high contrast should be used. Although our materials consist of high-contrast x-ray stereographs, appropriately taken stereophotographic pairs of wax plate reconstructions, plaster models, three-dimensional graphs, or similar materials could be used.

Three-dimensional perception has to do with the cortical fusion of two images which are separated approximately 3 degrees on each side of the mean optical axis when seen. Thus, two photographs taken so that they deviate in perspective approximately 3 degrees right and left from the normal will be perceived in three dimensions if the left eye sees only the left

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planar perspective and the right eye only the right.

The problem concerns the mechanics of presenting each eye with only one image, excluding the other. There are two principal means by which this can be accomplished. They are as follows: (A) Stereoscopic positive pairs of photographs *are separated* and observed through a binocular viewing device which through appropriate lenses limits each visual field to its respective image. This method is simple and very clear but not suitable for viewing by more than one person at a time. In addition, the areas observed are limited in size. (B) Stereoscopic pairs *are superimposed* to provide a double image within one frame of reference, each eye receiving the proper image by one of two means: *(1) Dichromatic filtration using complimentary colors.* This method utilizes double images which are superimposed—one red and the other either blue or green. If viewed through spectacles fitted with a red filter over one eye and a green or blue filter over the other, the red filter passes only the green image and likewise the green passes only the red. Thus each eye sees only one of the stereoscopic pairs; perception is three dimensional provided that the superimposed images are properly registered. The method is simple and can and has been used for publication, but there are several drawbacks with regard to color requirements. Filters and printing ink must match exactly and the method of printing must be carefully controlled to insure perfect register and exact deployment of ink on the printed surface. Similar objections apply to the use of color transparencies for projection purposes using the same method. Here differences in color temperature may alter the color balance of the transparency, causing a significant mismatch with respect to the filters, the color of each being fixed. *(2) Filtration of superimposed stereo images by polarizing filters.* Although this is the most complex of the methods listed, it has two virtues: it works and it is reproducible.

This method is a modification of the dye transfer color technique and initially was developed by the Polaroid Corporation for the production of black and white stereograms (Vectographs). At the time of this writing, the process has not been released except on an experimental basis.*

In general, the process adapted for the production of $3^1/_4$ by 4 inch Vectograph lantern slides can be divided into three stages.

a. The production of contact stereoradiographs (angiograms). The production of stereoscopic positive pairs from contact x-ray stereograms has been previously described by Hale and Reed.[1] Ordinarily, the matrix pairs from which the final Vectograph print is made could be exposed directly from the contact x-ray film. This would result in a positive matrix pair and a positive Vectograph lantern slide illustrating blood vessels as blue black structures. The introduction of an intermediate step prior to the printing of the matrix pairs reverses the final Vectograph print so that the projected three-dimensional image shows the blood vessels as clear areas against a dark background. This augments the perception of depth, increases the apparent contrast, and is less critical when processing the printing matrices or making the final Vectograph print. In addition, proper registration is more easily accomplished.

b. The development of stereo matrix pairs. The authors are accustomed to working with 8 by 10 inch Kodak matrix film. This is a specially treated dichromated bromide film which has the following unique characteristics. Exposure of this film is always made through the *back* (emulsion side down) so that the exposed dichromated gelatin emulsion is adjacent to the film support. During development and fixation the unexposed gelatin dissolves away, leaving a relief of the image, the thickness of retained gelatin being in proportion to the degree of exposure. This developed matrix film is subsequently bleached, washed, and dried. Although the detail in regard to the development and fixation of matrix film can be obtained from the Eastman Kodak Company, the following suggestions about contrast and exposure density pertaining to the illustration of blood vessels are offered: (1) In general, the thinner the exposed matrix film, the better the final Vectograph print.

*[illegible] Vectograph printing process [illegible] Polaroid Corporation [illegible]

since there is a tendency for small bubbles to collect in the valleys of a thicker matrix relief during the printing process. (ii) Registration of the matrices prior to Vectograph printing can be difficult, if not virtually impossible, since the silver image is bleached, removing visible points of reference. The authors have found that the following procedure eliminates this problem completely.

Identical areas of the original contact stereo x-ray negative pairs are projected onto 3¼ by 4 inch high contrast lantern slide plates. After the first plate has been exposed and fixed, the second of the paired stereograms is projected onto the developed surface of the first plate and oriented so that registration is exact. The developed plate is removed and the second positive plate exposed. This provides a properly



Fig. 1. A. Production of pre-registered positive plates for contact stereoangiogram. They are oriented in such a way to allow for the contact or projection exposure of matrix film. B. Eight by ten inch matrix film pair made from stereo positive plates and taped together on right border, emulsion to emulsion. Vectograph blank is inserted between during printing process.

registered stereo pair of 3¼ by 4 inch positive plates. Since the emulsion surface of the matrix film will contain the Vectograph ink during the final printing process, the two emulsion surfaces of the matrix pair are printed face to face with the Vectograph print blank in between. Thus the contact printed matrix exposure must be made from the lantern slide positives oriented in *mirror image fashion*. Fig. 1 *A* illustrates the appearance of properly taken and oriented positive plates. With this procedure three pairs of 3¼ by 4 inch positive plates oriented side by side can be printed simultaneously on single 8 by 10 inch matrix film. When developed, fixed, bleached and dried, this 8 by 10 inch matrix film is cut into three pieces across the 10 inch dimension producing three matrix pairs, the elements of each pair oriented side by side in mirror image fashion. These are then folded between stereo pairs forming a "book" with the emulsion side in. From these the final Vectograph prints are made.

c. The Vectograph printing process. The surfaces onto which the matrix images are transferred are laminated clear plastic. These surfaces contain appropriately oriented crystals which when treated with an iodine containing ink develop a deep blue color. During the manufacturing process the direction of polarity is rotated 90 degrees so that light from one free surface of the bilaminate plastic polarizes light at right angles to that transmitted from the opposite surface. The final print is made simply by soaking the matrix pair in Vectograph ink until the emulsion has softened and has absorbed the ink. The matrix pair emulsion to emulsion is drained and then laid on a flat surface. The upper leaf of the pair is raised and the clear dry Vectograph laminate inserted. An ordinary photograph roller is passed over the surface with moderate pressure slowly enough to express away bubbles caught between (Fig. 1 *B*). After a minute the laminate is removed and stabilized. The density of the blue black color can be varied by diluting the ink with distilled water. If a brown tint is desired the print can be made using a water wet laminate blank which will remain relatively colorless without stabilization. The ink stabilizer and Vectograph blanks can only be purchased directly from the Polaroid Corporation. Vectograph prints are viewed with transmitted light through polarizing spectacles.

These polarizing stereograms can be made any size. For purposes of demonstration 8 by 10 inch plates or larger can be set up in front of fluorescent view boxes. For projection purposes the 3¼ by 4-inch size seem to be best since smaller size lantern slides are difficult to register correctly. In addition larger projectors usually have a better capacity to illuminate the screen.

The ability to perceive a stereoscopic image requires that the eyes receive appropriately polarized images. Therefore polarized lantern slides cannot be projected onto a surface which depolarizes the reflected light and an aluminum screen has to be used in place of the ordinary glass beaded screen. With such a screen there is a tendency for glare to bother observers sitting near the optical axis of the lantern; observation is enhanced if the audience is dispersed laterally.

Results

It is not expedient to illustrate this communication with dichromatic or polaroid stereographs. These illustrative media are expensive to reproduce and are not justified by the limited objectives of this particular publication. In order to demonstrate the efficiency and sensitivity of the methods employed, a brief description of the circulation to the red nucleus and thalamus is presented; more detailed descriptions are the subject of comprehensive studies now being concluded.

Fig. 2 illustrates a positive contact radiograph (left hand illustration) of a section of brain 4 mm. thick passing through the interpeduncular fossa (*IP*) and foramina of Monroe (*F*). The level of section includes the oculomotor nerve (*N*). The plane of section is rotated about 30 degrees around the coronal plane. The intracerebral arteries appear as dark branched structures; no intracerebral veins are illustrated. Of particular interest is the distribution of the thalamic arteries: these vessels appear to be unique and terminal ... their distribution to



Fig 2 Composite illustration to show arterial supply (*left*) surface view of section (*right*) marked and labeled *CM*-central n *L* lateral n *SN* substantia nigra (*d*-diffuse *c*-compact) n *RN* red n *VL* ventrolateral n geniculate bod *O*-optic tract *P*-cerebral peduncle *I O* pon *Z* zona incerta Identified in the angiogram (*left*) illustrate the apparent unique arrangement of arteri l e el which I inch nd term n t s in p rticular 4 mm thick magn fication ×6



to illustrate loci of thalamic and extrapyramidal nuclei as follows *A* arcuate n *ANT* anterior n *C*-caudate n
Other structures labeled for purposes of orientation include *D*-dentate gyrus *G*-globus pallidus *L*-lateral
are *F* Foramen of Monroe *IP* interpeduncular fossa and *N*-oculomotor nerv Reference to the angiogram
nuclei area Stereoscopic examination fails to confirm arteries and veins of large size Paracoronal section

specific thalamic nuclei (see legend for identification). A similar situation prevails for the arteries of the red nucleus, substantia nigra, and cerebral peduncle. The vessels of origin are derived from the basilar arterial terminus, the distal part of the posterior communicating arteries, and the proximal posterior cerebral artery. These ganglionic radicles enter the posterior perforated substance and are distributed to the subthalamic, posterior thalamic and posteroinferior extrapyramidal nuclei.

The red nucleus is enclosed by a circumferential *network of terminal branches*. Specifically, this nucleus appears to have a dual supply connected by interarterial anastomoses, the large and small cell portions being more or less uniquely supplied.

The substantia nigra receives arterial blood from small arteries which perforate the cerebral peduncles. It appears that the compact portions of the substantia are supplied by lateral ganglionic radicles which originate from the posterior components of the circle of Willis, whereas the diffuse regions are supplied by more distal ganglionic vessels which originate from the posterior cerebral artery.

The question in regard to the terminal nature of the so-called ganglionic end arteries arises. If what we see illustrated in Fig. 2 is characteristic of the ganglionic cerebral circulation, then focal infarction of a single thalamic nucleus or part of a single nucleus might occur. Conversely, the presence of interarterial anastomoses of large caliber might prevent the development of a focal lesion. It is emphasized at *this point that a uniplanar photograph* cannot settle this question, especially where blood vessels cross one another at different levels within the section.

Fig. 3 illustrates the value of stereoscopic observation. The microcirculation of the red nucleus is presented and emphasizes the dual nature of the arterial supply. The inferior (lower) half of the nucleus is enveloped by a network of branches which originate from the basilar arterial terminus



Fig. 3. Stereoangiogram of the arterial supply to the nucleus ruber. Magnification ×5; section thickness 4 mm. Note two sets of arterial vessels, one originating from bevel to the medial aspect (*left*), the other consisting of several vessels entering from below. Large-caliber interarterial anastomoses are seen connecting these two sets of supply. Stereoscopic observation of the superior supply distinctly demonstrates the presence of a large anastomotic loop which connects primary ganglionic radicles.

and posterior communicating arteries. Numerous apparent anastomoses between end arteries can be identified. These are in reality points at which arterial vessels cross one another without anastomosis.

As far as the red nucleus is concerned, intra-arterial anastomoses between the superior and inferior sources of supply can be specifically identified. This is also the case for the components of the inferior circulation. Stereoscopic observation confirms the presence of a large caliber interarterial loop which connects two adjacent ganglionic arteries at the base of the nucleus. This observation is contrary to the concepts of Cohnheim,[2] Pfeifer,[3] and other more recent investigators using two-dimensional analyses. The relatively small size of Fig. 3 is necessary since the pair is intended to be viewed with the unaided eye, a card being placed between the individual illustrations so as to limit the visual perception of the right image with respect to the right eye and the left image with respect to the left eye. It is difficult for many to adjust to the accommodation requirements necessary for a successful observation. In general, the observer can best achieve the desired results if he adjusts for distant vision. There is one other reason for presenting this stereoscopic pair. This has to do with the hope that investigators interested in the cerebral microcirculation or the minute circulation of other organs, including the heart, lungs, kidneys, etc., might best develop their techniques if they were provided with a pre-registered positive print from which to copy. Although we do not wish to create the impression that the methods are unusually difficult, they do require attention to detail, and of these, proper registration of the matrices is the most important. This, by the way, becomes more critical as the magnification is increased, so that high orders of magnifications often require trial registrations and printings before suitable Vectograph prints result. We have been working on methods for the production of stereoscopic photomicrographs, but so far have not developed a reliable method.

Summary

Methods for the development of three-dimensional stereograms of cerebral blood vessels and the microcirculation of the human red nucleus have been presented. The method is reproducible and provides lantern slide material which an audience of 50 to 100 persons can view in three dimensions. Appropriately processed anatomic materials, wax models, three-dimensional graphs, and other photographic data which do not require full color can be used, and although the methods described were developed for the demonstration of cerebral blood vessels, they are applicable to the vasculature of any organ. The virtue of three-dimensional observation of the angioarchitecture of any organ cannot be appreciated fully until experienced.

Certain preliminary observations concerning the arterial circulation to the posterior thalamic and posteroinferior extrapyramidal nuclei are presented. The various nuclei seem to have a unique arterial supply without obvious intra-arterial anastomoses where that supply is dual and from a different parent vessel. When, as in the case of the nucleus ruber, part of the dual supply is derived from primary ganglionic radicles which originate from the same parent vessel, interarterial anastomoses of large caliber occur.

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A study of the etiological basis of primary pulmonary hypertension

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"Primary pulmonary hypertension refers to increased pressure in the pulmonary vascular bed resulting from intrinsic changes in the pulmonary vasculature. The lung parenchyma and heart are thought to be normal except for changes which occur secondary to the pulmonary hypertension. The clinical and pathologic appearances of this condition are well recognized and have been described by many investigators.[1-4]

It is not known whether the vascular lesions found in primary pulmonary hypertension represent the basic pathologic process or whether they result from pulmonary hypertension arising from an undetected disease, i.e., is primary pulmonary hypertension truly "primary"? Renewed interest in recurrent pulmonary embolization as a cause of pulmonary hypertension[4-7] has stimulated this clinicopathologic study of the possible relationship between multiple recurrent pulmonary emboli and primary pulmonary hypertension.

Materials and methods

Fifty-two patients with a diagnosis of primary pulmonary hypertension were seen at The Johns Hopkins Hospital from 1952 to 1962. Twenty-five were excluded from this study because of the existence of other lesions which might have produced the pulmonary hypertension (20 patients with congenital heart disease, 3 with emboli, 2 with pulmonary fibrosis). Four were eliminated from consideration because insufficient information was available to exclude other known causes of pulmonary hypertension.

Thus primary pulmonary hypertension was the diagnosis in 23 patients after cardiac catheterization, electrocardiographic, roentgenologic, and other special studies failed to reveal a cause for the pulmonary hypertension. Of these patients 9 died at The Johns Hopkins Hospital. Autopsies were obtained in all cases. These 9 cases constitute the basis of the present study. They represent all patients dying at this hospital with clinical primary pulmonary hypertension during the past 11 years.

Results

Several characteristics of the patients with this disease in the present series are listed in Table I.

The prominent symptoms are tabulated in Table II. Findings on initial physical examinations are presented in Table III. Summary of the electrocardiographic and roentgenologic findings are presented in Table IV. Data obtained by cardiac catheterization are given in Table V. The precipitating cause of death is shown in Table VI.

Patients ranged between 1 and 36 years

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Table I Characteristics of patients with primary pulmonary hypertension

Patient	Age (yr)	Sex	Race	Duration from onset to death (mo)
1	19	F	C	32
2	14	F	C	5
3	34	F	N	43 (minimum)
4	1	M	C	6–12
5	17	F	C	4
6	37	F	C	26
7	5	F	C	15
8	36	F	C	16
9	6	F	C	72

Table II Symptoms in 9 patients with primary pulmonary hypertension

Symptom	Number with symptom
Dyspnea on exertion	9
Syncope	[illegible]
Edema	6
Orthopnea	3
Chest pain	3
Dizzy spell	3
Cough	1

of age the average age at onset of symptoms was 16 2 years There were 8 females and 1 male Eight patients were Caucasian and 1 was Negro Duration of symptoms from onset to death ranged from 5 months to 6 years the average duration was 24 6 months

Most of the patients presented with dyspnea on exertion and syncopal episodes Systemic blood pressure was normal or low normal All had a systolic murmur usually heard best in the third intercostal space at the left sternal border A loud pulmonary second sound usually split was heard in 8 patients All had enlarged hearts and right axis deviation The hematocrit ranged from 39 to 54 the average was 46

Elevated pressures were recorded from the right atrium and ventricle and main pulmonary artery The average systolic pressure in the main pulmonary artery was 107 mm Hg Average diastolic and mean pressures were 55 and 69 mm Hg respectively In no instance was there evidence of a shunt Arterial oxygen saturations were above 90 per cent in all but 1 patient

Complete autopsies were obtained in 7 of the 9 patients Autopsy was limited to the thorax in the other 2 patients In no instance was a congenital heart lesion found Dilatation and hypertrophy of the right atrium and ventricle existed in all patients A dilated pulmonary artery was seen in 8 patients The foramen ovale was open in 2 and closed in 7 patients A mural thrombus was found in the right atrium of 1 patient The legs were not dissected in any of the patients

One patient had Laennec's cirrhosis and another had a fatty liver Except for

Table III Physical findings in 9 patients with primary pulmonary hypertension

Sign	Number with sign
Systolic blood pressure of 120 mm Hg or less	9
Systolic blood pressure of 100 mm Hg or less	5
Systolic murmur	9
Diastolic murmur	6
Loud pulmonary second sound	8
Edema	4
Vocal cord paralysis	1
Cyanosis	0
Clubbing	0
Leg vein thrombosis	0

Table IV Roentgenologic and electrocardiographic findings in 9 patients with primary pulmonary hypertension

Findings	Number
Roentgenologic	
Enlarged heart	9
Prominent pulmonary arteries	7
Peripheral pulmonary vasculature	
Normal	6
Decreased	2
Increased	1
Electrocardiographic	
Right axis deviation	9
Right ventricular hypertrophy	7

Table V Data obtained by cardiac catheterization in 9 patients with primary pulmonary hypertension

Patient	Pressure (mm Hg)					Arterial oxygen (% saturation)
	Main pulmonary artery	Right ventricle	Right atrium	Femoral artery	Wedge	
1	91/50 (64)		24/14 (19)			96 8
2	179/93	18[illegible]/3/11	(5)	11[illegible]/78	(61)	81
3	88/42 (55)	92/7 (35)			(10)	98 1
4		96/13 (50)	8/2 (4)			95
5	155/90 (119)	175/3/17 ([illegible]0)	(12)	(48)		94
6	106/40 (60)	101/3/14 (34)	12/6 (7)	112/70	(6)	9[illegible]
7	54/78 (35)	58/4/9 (16)	11/3 (4)			95
8	91/46 (60)	83/0 (40)	21/11 (14)	109/70	(6)	99
9	119/59 (87)	127/0/17 (53)	14/4 (8)	119/73		100

Mean pressures are in parentheses

acute or chronic passive congestion the liver was normal in the other 7 patients.

Findings in the lungs at autopsy are summarized in Table VII. Only the major change in the pulmonary vasculature is listed. Except for 1 case the changes were sufficiently widespread to account for the pulmonary hypertension. In the one case a necrotizing arteritis and mild thickening of the intima with connective tissue was seen in a small number of branches of the pulmonary artery.

Table VI Precipitating cause of death in 9 patients with primary pulmonary hypertension

Within 24 hr of cardiac catheterization	4
Within 24 hr of operative procedure	3
Gastrointestinal bleeding	1
Progressive congestive heart failure	1

Table VII Major changes in pulmonary vasculature seen in 9 patients with primary pulmonary hypertension

Organizing and recanalized pulmonary emboli or thrombi	3
Recanalized pulmonary emboli or thrombi	3
Subintimal connective tissue proliferation	1
Severe arteriosclerosis	1
Necrotizing arteritis with subintimal thickening	1

In 6 of the 9 cases widespread organizing or recanalizing pulmonary emboli or thrombi were seen. In 1 other case subintimal thickening of the muscular arteries was present. In several of the cases the intravascular clot seemed to be clearly embolization and not thrombosis. In 1 patient (Patient 1) the left pulmonary artery and three of the six major branches of the right pulmonary artery were occluded by old densely adherent clots of all ages. Myriads of emboli from recanalized to recently organized ones were evident. In another patient (Patient 8) there were multiple intravascular clots. The stages from fresh blood clot to completely recanalized arteries which were indistinguishable from arteriosclerosis and intimal thickening could be traced. The characteristic appearance of fresh and recanalized intravascular clots in these patients is seen in Figs. 1 and 2.

Thus in 6 of the 9 cases changes compatible with multiple pulmonary emboli were found.

Discussion

It is difficult to determine whether the reorganized clot seen in the pulmonary vasculature of patients with pulmonary hypertension represents thrombus formation secondary to primarily damaged vessels or whether it represents multiple pulmonary emboli. Multiple pulmonary emboli can result in changes which are







Fig. 1. These figures [illegible] show the [illegible] appearance [illegible] of [illegible] from [illegible] several patients in the series with the clinical diagnosis of primary pulmonary hypertension.

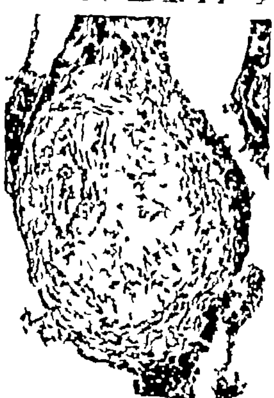


Fig. 2. [illegible] small pulmonary [illegible] from patients in the series with the [illegible] of primary pulmonary [illegible]

morphologically indistinguishable from the subintimal thickening seen in primary pulmonary hypertension. This has been clearly established experimentally.[8,9] Cases of multiple pulmonary emboli resulting in extensive fibrous intimal proliferation ... marked medial hypertrophy and clinically puzzling pulmonary hypertension have been reported.[10,11]

Of the 9 patients considered herein, exhaustive clinical studies could not differentiate between primary pulmonary hypertension and recurrent pulmonary emboli. Autopsy findings were also not conclusive. Clinically, these two conditions present much the same appearance, and indeed may be the same disease. Patient 8 represents an example of this. She was in good health until age 35, when she experienced a sudden episode of syncope followed by 16 months of increasing dyspnea, weakness, and fatigue which terminated in her death. This story is characteristic of both the primary disease and progressive pulmonary hypertension secondary to recurrent pulmonary emboli.

A recent thorough study of recurrent pulmonary emboli by Wilhelmsen[7] helps clarify the similarity of this disease to primary pulmonary hypertension. In 10 cases of recurrent pulmonary emboli studied by him, progressive dyspnea, absence of signs in the lower extremities, loud pulmonary second sound, right ventricular hypertrophy by electrocardiogram, and catheterization findings of increased pulmonary arterial and normal wedge pressures were found. The data presented are almost identical to the data for the patients whose cases are discussed in this paper. The short course of the disease from onset of symptoms to death is notable in this and in Wilhelmsen's series. The duration of the illness ranged from one-half to 6 years, with an average of 2.5 years for the patients of the present series and 3.1 for Wilhelmsen's. The average age of the latter group, however, was 53.9 years in contrast to 16.2 years for the 9 patients of the present study.

In many instances the differential diagnosis between these two entities has seemed to revolve about the presence or absence of findings in the legs indicative of thrombophlebitis. It is well known that approximately 50 per cent of the patients with pulmonary emboli do not exhibit findings of venous disease in the lower extremities,[7] although over 95 per cent of emboli are thought to originate from the lower extremities. Silent thrombi of the leg veins was demonstrated by Roessle,[1] who performed extensive dissection of the legs during 324 routine autopsies in patients who were over 20 years of age. Roessle found thrombi in the veins of the calf in 27.1 per cent of the patients. Hampton and Castleman,[12] studying pulmonary infarction, stated that "a very large percentage of the (pulmonary) emboli arise from symptomless thromboses of the deep veins of the legs, usually in the popliteal region." Thus, the criterion of thrombosis in the leg veins is not a good one on which to base the differentiation of recurrent pulmonary emboli from primary pulmonary hypertension.

Since many, if not all, patients with a diagnosis of primary pulmonary hypertension may represent cases of recurrent pulmonary emboli, all should be treated as such. Anticoagulants and venous ligation are the treatments of choice. Neither have been given an adequate trial. Rigorous therapy to prevent recurrent embolization may arrest the progress of many cases otherwise considered to be "primary" pulmonary hypertension. Other forms of therapy have not affected the relentless short course of this disease. Anticoagulants offer the added advantage of helping to prevent the formation of thrombus in pulmonary vessels already damaged by arteriosclerosis.

Summary

Clinical and autopsy findings are discussed in 9 patients in whom a diagnosis of primary pulmonary hypertension was made. In 6 of these cases, pulmonary emboli and thrombi provided the etiologic basis for pulmonary hypertension. The difficulty of differentiating cases of recurrent pulmonary embolization from cases of primary pulmonary hypertension is discussed. The possibility that all cases of primary pulmonary hypertension represent recurrent embolization is considered. Therapy with anticoagulation and venous ligation is recommended for all

cases of primary pulmonary hypertension

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Experimental and laboratory reports

Postmortem angiographic studies on the coronary arterial circulation

Incidence and topography of occlusive coronary lesions relation to anatomic pattern of large coronary arteries

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This paper is one of a sequence of reports on various aspects of coronary artery disease in Boston City Hospital (BCH) autopsies studied by a modification[1] of Schlesinger's coronary injection plus dissection method. It deals with the incidence of coronary occlusions, their topography, and their relationship to anatomic variations in coronary arterial pattern. As in other papers of the series,[2-4] the main comparisons are drawn with similarly obtained data reported by Schlesinger and his associates from the Beth Israel Hospital (BIH), Boston.[5-7] It seemed to be worth while to determine to what extent their findings in an autopsy population largely Jewish hold true for one of a different ethnic and socioeconomic composition drawn from the same metropolitan area. Limited comparisons are also made with data from noninjected BCH hearts in order to assess the gain derived from the injection technique over the conventional method of inspection for examining coronary arteries.

Materials and methods

BCH cases studied by injection method. The BCH cases studied at autopsy by coronary injection have been described previously.[2] They are characterized by sex, race, and age in Table I. Two thirds of the subjects were at least 60 years old. Eleven were Jewish, and 419 were Chris-

Table I. Data on race, sex, age, and evident incidence of coronary occlusions for 430 injected and 430 noninjected BCH hearts

	Injected	Noninjected
Males	238	236
Females	192	194
Chinese	2	0
Negroe	56	37
Whites	372	393
Age range (yr.)	13 to 96	18 to 96
Mean age (S.D.)	65 (14)	68 (13)
Hearts with occlusions	103	44
Number of occlusions	277	65

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tian These autopsies were performed over the years 1957 to 1959 and are not consecutive The hearts of infants those of patients in medicolegal cases and those of patients with active tuberculosis were deliberately excluded but otherwise the series is unselected

The coronary arteries were injected with a radiopaque mass the heart was unrolled x ray films were taken and the coronary arteries were dissected with the angiograms as guides The injection pressure used was 200 mm Hg The ventricles were coronally sliced at intervals of 0.5 cm Stereoscopic angiograms of the slices were prepared Findings in the coronary arteries and the myocardium were recorded in detail on tracings superimposed on the x ray film The technique allows complete visualization and careful study of the coronary arterial tree

The method of examination of the coronary arteries follows that of Schlesinger except for two modifications the radiopaque mass employed was not lead phosphate-agar but barium sulfate-gelatin[3] and in unrolling the heart the interventricular septum was not extirpated but left intact These technical modifications do not impair comparisons with Schlesinger's data

Noninjected BCH cases Noninjected hearts from contemporary routine BCH autopsies comprised a control group similar in size and age sex and race characteristics to the group of injected hearts (Table I) These autopsies were performed over a period of about 5 months in 1957 and (except for the exclusion of infants medico legal cases and patients with active tuberculosis) are consecutive Various prosectors examined the coronary arteries in these noninjected hearts by conventional methods of serial transverse sectioning The prosectors were not at the time aware that the results of their examination were to be analyzed for this report

Observations

Incidence of occlusions Among the 430 injected BCH hearts those with coronary occlusions numbered 103 (24 per cent) of which 73 (males 44 females 29) had only old occlusions 17 (males 10 females 7) had both old and recent occlusions and 13 (males 8 females 5) had only recent occlusions All but a few of these hearts with occlusions had also severe atherosclerosis narrowing elsewhere in the coronary arterial tree

Many more coronary occlusions were demonstrated in the group of injected hearts than in the control group of noninjected hearts recorded were two and one half times more hearts with occlusions and three and one half times more occlusions in the former (Table I) The difference holds for various age sex categories (Table II)

A close similarity obtains between the present series of 430 injected BCH hearts and the 1941 BIH series of 400 injected hearts[4] (Table II) In both these samples there were more males than females and the majority belonged to the older age groups Interhospital differences in the incidence of coronary occlusions occur in individual age sex categories but the over all incidence of occlusions is the same for both series and so is the average number of occlusions per heart There were 227 occlusions in 103 injected hearts of the BCH series (2 2 occlusions per heart) and 198 occlusions were contained in 94 hearts of the 1941 BIH series (2 1 occlusions per heart) [4]

In Table III injected BCH hearts with single occlusions and with multiple occlusions are listed separately by sex and age It will be noted that hearts with multiple occlusions were more numerous than those with single ones that females showed a greater proportion of hearts with multiple occlusions than did males and that the number of occlusions tended to be no greater among the very old than among the relatively young

Site of occlusions Table IV shows the distribution of occlusions observed in the main stems and branches of the coronary tree in injected and noninjected BCH hearts and in injected BIH hearts (1941 series) [4] In each vessel category the number of occlusions found was less in the noninjected than in the injected hearts the discrepancy being greater for the coronary branches than for the main stems In contrast a close numerical correspondence in all vessel categories

*Table II. Incidence of coronary occlusions by sex and age in injected and noninjected BCH hearts and in injected BIH hearts (1941 series)***

Age (yr.)	Noninjected BCH: Number of hearts	Noninjected BCH: Number with occlusion	Injected BCH: Number of hearts	Injected BCH: Number with occlusions	Injected BIH (1941): Number of hearts	Injected BIH (1941): Number with occlusions
Male						
< 20	(1)	—	(2)	—	—	—
20-39		0 (0%)	8	0 (0%)	44	1 (2%)
40-59	50	6 (12)	44	10 (23%)	85	20 (24%)
60-79	14	16 (11)	153	42 (28%)	115	43 (37%)
80 on	36	3 (12)	31	10 (32%)	9	4 (44%)
20 on	235	25 (11)	236	62 (26%)	253	68 (27%)
Female						
20	194	19 (10)	191	41 (21%)	147	26 (18%)
20-39	4	0 (0)	7	1 (14%)	19	1 (5%)
40-59	41	3 ( )	38	8 (21%)	56	2 (4%)
60-79	106	8 (8)	93	16 (17)	65	21 (32%)
80 on	43	8 (19)	53	16 (30%)	7	2 (29%)
< 20	—	—	(1)	—	—	—
Total	429	44 (10%)	427	103 (24%)	400	94 (24%)

**BCH hearts from subjects less than 20 years of age were excluded from the computations.

Table III. Incidence of single and multiple coronary occlusions in injected BCH hearts grouped by sex and age

Ages (yr.)	Sex	Hearts with single occlusions	Hearts with multiple occlusions	Totals
70 to 89	Males	14 (44%)	18 (56%)	32
	Females	9 (38%)	15 (6 %)	24
	Both	23 (41%)	33 (59%)	56
Less than 69	Males	14 (4 %)	16 (53)	30
	Females	6 (35%)	11 (65%)	17
	Both	20 (43)	27 (5 %)	47
All	Males	28 (45)	34 (55)	62
	Females	15 (37)	26 (63%)	41
	Both	43 (42%)	60 (58%)	103

hold between the injected hearts of the BCH and 1941 BIH series.[8] In both series two thirds of all the occlusions were in the coronary artery main stems and a third were in the branches. The distribution of the right coronary artery (main stem plus branches) was involved by the occlusive process at least as often as the distribution of the left anterior descending coronary artery and that of the left circumflex artery was involved less often than either. Similar trends were shown by injected hearts from males and females (Table IV) and by injected BCH hearts with single occlusions (Table V).

It is of interest that a different distribution of occlusive lesions was observed in another BIH series reported in 1949.[7] Among the 976 hearts of this BIH series the incidence of occlusions in the primary

branches was one quarter of that in the first 4.0 cm. of the main stems of the coronary arteries and one half of that in the distal segments of the main stems. Among the injected BCH hearts the number of occlusions lodged in the coronary branches (which is 76) was two thirds of that in the first 4.0 cm. of the main stems (112) and almost twice that in the distal parts of the main stems (40).

Distances from coronary ostium. Fig. 1 presents detailed data on the lengths of the vessel segments intervening between either of the coronary ostia and the occlusions among injected hearts of the BCH series and those of the 1941 BIH series.[4] Among BCH hearts two thirds of the occlusions in coronary main stems and branches occurred within 4.0 cm. of the coronary ostium; more occlusions ranged

Table IV. Distribution of occlusions in the main stems and branches of the coronary arteries of injected and noninjected BCH hearts and of injected BIH hearts (1941 series)

Group	All main stems	All branches	Main stem of: RC	Main stem of: LC	Main stem of: LD	Branches of: RC	Branches of: LC	Branches of: LD
BCH Males	93 (70%) *36*	39 (30%) *1*	46 (35%) *14*	19 (14%) *10*	28 (21%) *12*	9 ([illegible]) *0*	13 (10%) *1*	17 (13%) *1*
BCH Females	59 (67%) *2?*	36 (38%) *5*	[illegible]6 (26%) *9*	15 (16[illegible]) *3*	18 (19%) *10*	8 (9%) *1*	13 (14%) *3*	15 (16%) *1*
BCH	152 (67%) *38*	75 (33%) *7*	[illegible]2 (32%) *23*	34 (15[illegible]) *13*	46 (20[illegible]) *2?*	1? (8%) *1*	26 (11%) *4*	32 (14%) *2*
BIH (1941)	134 (68%)	64 (32%)	46 (23%)	36 (18%)	5? (?6%)	24 (1?%)	16 (8%)	24 (12%)

Numbers [illegible] italics pertain t[illegible] [illegible]njected BCH hearts. RC, Rig[illegible] [illegible] [illegible]nary artery; LC, Left circumfl[illegible] coronary artery; LD, Left ant[illegible] descending co[illegible]nary artery.

Table V. Distribution of single occlusions in the main stems and branches of the coronary arterial tree in 43 injected BCH hearts

Sex	All main stems	All branches	Main stem of: RC	Main stem of: LC	Main stem of: LD	Branches of: RC	Branches of: LC	Branches of: LD
Males (28 cases)	23 (83[illegible])	5 (17[illegible])	14 (50[illegible])	1 (4[illegible])	8 (29[illegible])	—	—	5 (17[illegible])
Females (15 cases)	10 (67[illegible])	5 (33%)	6 (40%)	2 (13.5[illegible])	? (13.5[illegible])	1 (6[illegible])	2 (13.5[illegible])	? (13.5%)
Total (43 cases)	33 ([illegible]7%)	10 (23%)	20 (47%)	3 (7%)	10 (23[illegible])	1 (2%)	? (5%)	7 (16%)

RC, Right coronary artery; LC, Left c[illegible] [illegible] [illegible] [illegible]ary artery; LD, Left [illegible] descending [illegible] [illegible]nary artery.

farther from the coronary ostium in the right coronary main stem than in the other vessels and males and females did not differ in these respects. The distances measured between the coronary ostium and the main stem occlusions proved to be similar for the BCH and BIH series.[4]

Among noninjected BCH hearts the distances from the coronary ostia of 31 of the occlusions were recorded by various prosectors and of these measurements only one exceeded 4.0 cm.

Length of occlusion. Fig. 2 presents data on the lengths of the occlusions in the injected BCH series and the 1941 BIH series.[4] The lengths of the occlusions showed no differences between the sexes in the former.

In both series the lengths of most of the occlusions were 1.0 cm. or less and a

Table VI. Incidence of coronary occlusions in relation to coronary pattern and sex in injected BCH hearts and in BIH hearts (1941 series)[4]

Coronary pattern	Sex	BIH series (1940)		BCH series			
		Number of hearts	Number with occlusions	Number of hearts	Number with occlusions	Number of occlusions	Number of occlusions per heart
I	Males	68	25 (37%)	151	40 (26%)	88	2.2
	Females	40	11 (27%)	120	25 (21%)	46	1.8
	Both	108	36 (33%)	271	65 (24%)	134	2.1
II	Males	47	13 (28%)	45	13 (29%)	26	2.0
	Females	29	1 (3%)	41	7 (17%)	27	3.9
	Both	76	14 (18%)	86	20 (23%)	53	2.7
III	Males	30	12 (40%)	42	9 (21%)	18	2.0
	Female	11	3 (27%)	31	9 (29%)	22	2.4
	Both	41	15 (37%)	73	18 (25%)	40	2.2
Total	Both	225	65 (29%)	430	103 (24%)	227	2.2

Table VII. Sites of coronary occlusions in relation to coronary pattern and sex in injected BCH hearts

Coronary pattern	Sex	Number of occlusions in					
		RC and branches	LC and branches	LD and branches	RC	LC	LD
Right preponderant	Males	38 (43)	15 (17)	35 (40%)	30 (34%)	10 (11)	21 (24)
	Females	19 (41)	11 (24)	16 (35)	14 (30%)	8 (17%)	10 (22)
	Both	57 (43)	26 (19)	51 (38)	44 (33)	18 (13)	31 (23)
Balanced	Males	10 (38)	10 (38)	6 (24)	9 (35%)	4 (15)	4 (15)
	Females	8 (30%)	11 (40%)	8 (30%)	6 (22%)	4 (15%)	4 (15)
	Both	18 (34%)	21 (40%)	14 (26)	15 (28%)	8 (15)	8 (15)
Left preponderant	Males	7 (39%)	7 (39)	4 (22)	7 (39)	5 (28)	3 (17)
	Females	7 (32)	6 (27%)	9 (41)	6 (27%)	3 (14)	4 (18)
	Both	14 (35)	13 (32.5)	13 (32.5)	13 (32.5)	8 (20)	7 (18)

RC, Right coronary artery; LC, Left circumflex coronary artery; LD, Left anterior descending coronary artery.

larger proportion of short occlusions occurred in the branches than in the main stems but the BIH measurements tended to be smaller Occlusions less than 0 3 cm in length comprised one twentieth of the total number of occlusions in BCH hearts (15/227) and one fourth of that in BIH hearts (77/209) those 0 5 cm or less comprised one third of the occlusions in the former (76/227) and well over one half of those in the latter (122/209)

Among the noninjected BCH hearts the lengths of 23 of the occlusions were recorded all of which were less than 0 3 cm

Incidence of occlusions in relation to coronary pattern Injected BCH hearts were classified into three groups according to the coronary patterns described by Schlesinger[4] *Group I or right preponderant hearts* are those in which the right coronary artery supplies the ipsilateral ventricle the posterior part of the interventricular septum and a substantial part of the left ventricle *Group II or balanced hearts* are those in which the right coronary artery supplies the right ventricle plus the posterior part of the ventricular septum and the left coronary artery supplies the left ventricle plus the anterior part of the interventricular septum *Group III or left preponderant hearts* are those in which the left circumflex coronary artery supplies at least in part the posterior portion of the interventricular septum

Table VI gives the relationship between the incidence of occlusions and the coronary pattern in males and females of the injected BCH and the 1940 BIH series[3] The number of occlusions per heart was similar in all groups among BCH males and females Among BIH females the number of hearts with occluded coronary arteries was relatively smaller in Group II than in Groups I or III but no such difference between groups was demonstrable among BCH females and BCH and BIH males A separate analysis limited to White subjects of the BCH series showed that both the number of hearts with occlusions and the number of occlusions per heart were similar for Groups I II and III

Sites of occlusion in relation to coronary arterial pattern In Table VII the sites of occlusion in the injected BCH hearts are separately listed by sex and coronary pattern In Groups I and II the distributions of occlusions in various elements of the coronary tree differed in that the left circumflex artery and its branches were more frequently the site of occlusions in the latter group No other significant difference in the distribution of occlusions was found between groups or between sexes within each group

The distribution of main stem occlusions in Group I hearts of the BCH series was similar to that shown by the corresponding group included in the 1941 BIH series[6] (Table VIII)

Discussion

Schlesinger's work has shown that unaided dissection of noninjected coronary arteries may fail to disclose many of the occlusions present in a given series of specimens[4] and this we have confirmed If one assumes the number of occlusions

Table VIII Incidence of coronary occlusions in the coronary artery main stems of right preponderant hearts of the injected BCH and (1941) BIH series[6]

Series	Number of hearts	Number of occlusions (%): RC main stem	LC main stem	LD main stem	All main stems
BCH	271	44 (16)	18 ( )	31 (11%)	93 (34%)
BIH (1941)	207	24 (12%)	19 (9)	26 (13)	69 (34

RC Right coronary artery LC Left coronary LD Left anterior descending coronary artery

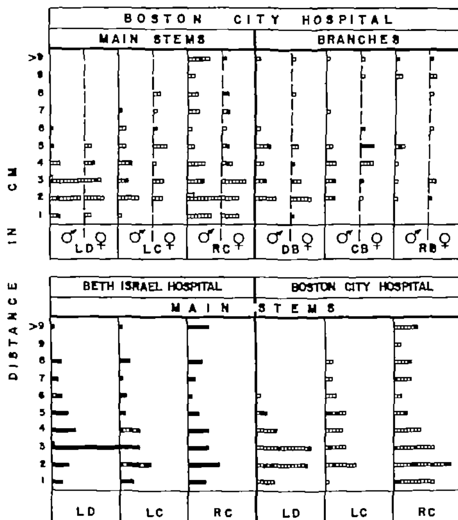


Fig. 1. Distribution of the lengths of the vessel segments intervening between coronary *ostium and occlusions in injected hearts of the B.C.H. series and in those of the (1941) B.I.H. series.*

found in our injected hearts to be similar to that in the noninjected control hearts, the proportion of occlusions missed in the latter comprises as much as two thirds of the total, and the number of control hearts in which occlusions were found underestimates the correct figure by more than half. As might be expected, the occlusions not shown by routine methods of study appear to be mostly those far from the coronary ostia and in the coronary branches rather than in the main stems. Contrary to expectations, the data suggest also that the occlusions missed are by no means invariably short, and many of them probably exceed half a centimeter in length.

A limitation of the experimental design here used to assess the relative accuracy of the injection and the routine methods for demonstrating coronary occlusions is the fact that the control hearts, unlike the injected ones, were examined by prosectors who did not have the publication of results in mind. Nevertheless, we share Schlesinger's view that the disparity in the results obtained with the two methods is less a matter of the care with which specimens are processed than it is of the adequacy of the technique of examination.[3,4] With noninjected hearts our own experience as prosectors has been that it is practically impossible, even with the most painstaking care, to dissect and fully

expose for study more than a fraction of the coronary arterial tree particularly when this is diseased. Review of the literature indicates that coronary injection techniques are as yet not in common use. Unless the examination of hearts in routine autopsies elsewhere is done much more adequately than appears to have been true in our laboratory, it would seem safe to assume that the autopsy data now on record which bear on the incidence and topography of coronary occlusions include gross inaccuracies. In this connection it is of interest to note that the incidence of coronary occlusions (10 per cent) in our series of noninjected hearts from Boston City Hospital proved to be no smaller than that in routinely studied cases reported from the Beth Israel Hospital (10.5 per cent) or from the other two Boston hospitals (11 and 7.5 per cent) cited by Schlesinger.[6]

The pattern of occlusive coronary artery disease demonstrated by the injection method proved to be remarkably similar for the BCH hearts and those of the BIH (1941) series.[4] The correspondences between the two series include the proportion of hearts with occlusions, the average number of occlusions per heart, the vessels involved by the occlusive process, and the distances intervening between the occlusion and the coronary ostium. These same correspondences were noted to a large extent also between BCH males and females, and it was found that the sites favored by the occlusive process held true for the initial (i.e., single) occlusion as for the subsequent (multiple) ones. The list of correspondences between BCH and

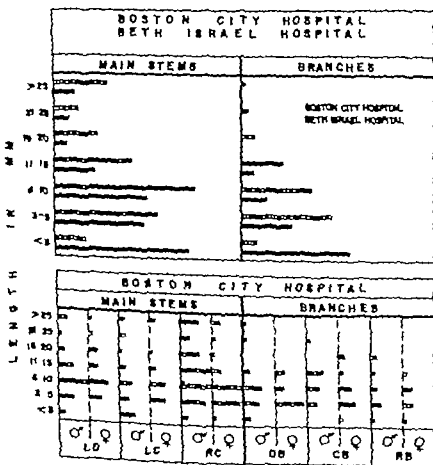


Fig. 7. Distribution of the lengths of the coronary occlusions in injected hearts of the BCH series and in those of the (1941) BIH series.[4]

BIH data probably includes also the lengths of the occlusions. Although the pertinent values recorded at Beth Israel Hospital tended to be generally smaller than those at our laboratory, this fact loses significance when one considers that the limits of a given occlusion are not abrupt, so that the subjective factor inevitably determines where precisely one's measurement of its length is to begin and end.

Aside from the fact that the BCH and the 1941 BIH series which we compared were studied some two decades apart, the *many correspondences outlined between* them are noteworthy, in that the BIH population was largely Jewish[8] and the BCH population was largely Christian. That these correspondences are all coincidental cannot be ruled out as a possibility, however, for a very different localization of coronary occlusions was shown by another BIH series reported in 1949.[7] To clarify the matter it would seem obvious that more work is needed, and that comparisons between ethnic groups themselves rather than between hospital populations is called for here.

The relation of anatomic pattern to pathologic conditions of the coronary arteries has been studied and considered to be significant by Schlesinger.[5] From his study he concluded that hearts in which the left coronary artery predominates (Group III) suffer most from the effects of coronary atherosclerosis, those with a balanced circulation (Group II) suffer least, and those with a right preponderant circulation (Group I) are intermediate in this respect between the other two groups. This conclusion was derived from relationships he demonstrated between the coronary artery pattern and the incidences of (a) recent and healed cardiac infarcts, (b) coronary atherosclerotic narrowing, and (c) coronary occlusions. The BCH data presented here which bear on this matter pertain solely to the third of these relationships, and indicate that coronary occlusions occur as often in hearts with one type of coronary pattern as in those with another. Both the proportion of BCH hearts with occlusions and the number of occlusions per heart proved to be similar for groups of cases with a right preponderant, a balanced, and a left preponderant coronary pattern.

Another relationship here explored is that between the coronary pattern and the distribution of occlusions in various component parts of the coronary tree. It was thought of interest to determine whether the frequency of occlusions in a given vascular territory bears a direct relationship to the size of the latter. If such a relationship exists, a greater proportion of occlusions would occur in the right coronary artery in Group I hearts than in Group II and III hearts, and *by the same token, the reverse of this* would hold true for the left circumflex artery. This relationship was not consistently shown by our material. Although the left circumflex artery was found to contain proportionately fewer occlusions in Group I hearts, in which this vessel is rudimentary, than in Group II hearts, in which it is better developed, no other statistically significant difference in the relative number of occlusions among the major coronary divisions was demonstrable between groups. It appears that, in regard to the frequency of coronary occlusions, whether the distal segment of a given coronary artery is long or short does not very much matter generally, because the majority of occlusions lodge close to the coronary ostia. To this tendency for occlusions to be proximal Schlesinger[5] attributes his finding that in Group I and III hearts the number of occlusions per unit length of vessel was highest in the left circumflex or the right coronary artery, whichever of these two vessels happened to be rudimentary.

The tendency for occlusions to occur in the proximal segments of vessels was manifest in the main stems and branches, but more so in the main stems. Among the main stems this tendency seems to be least pronounced in the right coronary artery. It was found that (the length of the vessel permitting) more occlusions ranged farther from the coronary ostium in the main stem of the right coronary artery than in the main stems of either the left circumflex or the left anterior descending arteries, and this finding was consistent in both the BCH and 1941 BIH series[8] and in BCH hearts of either

sex. We do not have a satisfactory anatomic or hemodynamic explanation to offer for this greater spread of occlusions in the right coronary artery than in the left but what does seem clear is that the reason is not that the right coronary artery is longer. Schlesinger's measurements show that on the average the right coronary artery is substantially shorter than the left anterior descending artery even in hearts in which the former is considered to be preponderant.[8]

Summary

An angiographic study of 430 non-selected hearts disclosed 3½ times more coronary occlusions and 2½ times more hearts with occlusions than were found in control routine autopsies.

The 430 hearts studied were from 372 whites, 56 Negroes, 2 Chinese; 238 men, 192 women. Mean age was 68 (S.D. 14) years; two thirds were at least 60 years old. All but 11 subjects were Christian. Hearts with occlusions numbered 103; number of occlusions was 227.

The topography of occlusions demonstrated angiographically was similar for either sex. The majority of occlusions were short (0.5 cm. or less). Two thirds were lodged within 4.0 cm. of the coronary ostia. Coronary main stems were occluded twice more often than branches. The right coronary arborization was occluded as often as that of the left anterior descending; that of the left circumflex was occluded the least often. Occlusions in the right coronary main stem ranged farther away from the coronary ostium than those in the other main stems. The same sites in the coronary tree were favored by solitary occlusions and multiple ones. Occlusions occurred as often in hearts with (Schlesinger's) balanced coronary pattern as in those with a right or a left preponderant pattern. Occlusions did not involve the preponderant coronary more often than other coronaries.

The demonstrated incidence and topography of coronary occlusions in this series resemble those reported for another series largely Jewish similarly studied by M. J. Schlesinger over 2 decades ago.

Addendum

New data from Beth Israel Hospital published after completion of this report show that the coronary artery pattern is not related to prognosis after infarction, incidence or location of coronary occlusions, or severity of coronary atherosclerosis.[11]

Injected specimens were prepared by Olga Fedotova Connolly and Sandra J. Fish, A.B. G. Kenneth Mallory, M.D., Professor of Pathology, Boston University School of Medicine and Director, Mallory Institute of Pathology, Boston City Hospital, read the manuscript critically and offered helpful suggestions.

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High frequency shin bar ballistocardiograms, a method of greatly improving simple shin-bar records

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The shin bar method originally proposed by Dock and associates[1] possessed a simplicity which made it available to a host of doctors and it has been widely used. Unfortunately, as is the case with so many simple clinical methods, increasing understanding of the physical factors involved has disclosed serious difficulties.[2,3,4]

But the recent studies also point to a possible remedy: if the frequency of the body's movements on its supports could be raised materially, a very much better record of the forces of the circulation could be secured by recording body movements with a shin bar. This was recognized over 10 years ago by Walker and associates,[2] who improved their shin bar records by fixing the subject with sand or putty, a method not very practical for routine clinical work. More recently, Noordergraaf, by lying on a nonslip pad with his feet tight against a wall, increased the *frequency of his body's movement on its supports* from 3.6 to 5 cycles per second, and great improvement in the shin bar record resulted in the one subject tested, himself. Also Tumanovsky and Sifonov,[4] by placing their subjects on a cotton mattress, raised the frequency of the body's *on its supports from 5 to 10.5 cycles per second* in the instance illustrated, and great improvement in shin bar records resulted. Although the degree of improvement reported by the Russians was greater than we were able to secure on one of the cotton mattresses used in our hospital—doubtless because the physical properties of the Russian mattresses were different—the Russian experience and that of Walker and associates,[2] of Reeves and associates,[5] and of Noordergraaf[3] encouraged us to seek an easy and practicable means of improving shin bar records by raising the frequency of the movements of the body on its supporting surface.[6] We planned to judge the degree of success attained by comparing our improved high frequency (HF) shin bar records with ultralow frequency (ULF) force records obtained on the same subjects.

Apparatus

Our ULF instrument has been described.[7] To secure high frequency shin bar records we used a shin bar of balsa wood that weighed 105 grams (a still lighter shin bar of 33 grams gave identical records and was less convenient). This bar was bound

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to each shin of the subject by a rubber strap. A metal pointer attached to the shin bar impinged on a button in the center of an air filled tambour of 3 cm. diameter attached by a short rubber tube to the head of a Sanborn blood pressure transducer leading through a Sanborn amplifier No. 311 to a Sanborn Twin Viso recorder. The recording system* had a natural frequency of about 100 per second.

To study the effect of known forces on our records a weight was suspended from the ceiling from a position over the subject's waist. When pulled back and allowed to rest against his head, it exerted a force feetward which, when m = its mass and θ = the angle of the string with the vertical, was $F = m \sin \theta$. When with the record running and the subject holding his breath the weight was abruptly removed from the head, an easily measured deflection of the base line resulted.

In various experiments we tried many things between the floor and the patient: a nonslip pad of synthetic rubber (sold to prevent small rugs from slipping on a polished floor), several layers of this pad, sheets of polyethylene foam that were 5, 10, and 20 cm. in thickness, an air mattress inflated to different air pressures, two such mattresses one on top of the other, a cotton mattress 16 cm. thick, and an inner spring mattress of the kind used on hospital beds.

Methods

Standard Dock shin bar records were secured with the patient lying supine on the floor both with and without a roller under his Achilles tendon, the feet being free.

To secure high frequency shin bar records the final technique was as follows: Three sheets of the nonslip rubber pad were placed on the floor near a substantial wall. The subject first lay on the pad with his knees bent and his feet touching the wall or a heel piece placed against the wall with his head on a small pillow. Then by extending his knees the subject forced his back headward against the friction of the pad, a movement which pulled on his clothes and skin and produced a sensation of tightness both in the heels and back which persisted during the test. The success of the tightening was determined by estimations of the frequency of the movement of the subject's body on its support made by pushing on his head and rapidly releasing the thrust while the record was running. After the selection of a test at which interference from the waves of the ballistocardiograph was minimal, the frequency and the degree of damping were readily determined.

Ultralow frequency records were taken immediately before or after the shin bar records. The subjects used were medical students, staff, and patients at the University hospital, 44 in number.

Results

It was soon discovered that to get shin bar records which resembled ULF records one must get the body frequency up over 6.5 cycles per second. When the subject simply lay on a mattress or on one of the other articles enumerated, the frequency was raised a little but not enough. Only by having the feet firmly against the wall did we secure a satisfactory tightening. To this tightening the nonslip pad placed under the subject contributed more than the mattresses used, and we finally standardized the technique by using several layers of this pad between floor and subject.

In Table I one can compare the frequency of the body movement on its supports in 20 subjects, each studied under three conditions: (1) when lying on the floor with a roller under the heels and the feet free, (2) when lying on the floor without the roller and with the feet free, and (3) when the frequency had been raised by applying the heels to the wall according to the method described. The frequency and damping of the movements of our subjects on the floor with the feet free are similar to the values given by Tannenbaum and associates. After the subject has been tightened, the frequency is always substantially increased, indeed it is often more than doubled. The difference is statistically significant.

In addition to increasing the frequency, the HF shin bar technique greatly increases the damping over that present in the original Dock procedure. In 4 patients we

*M. Gentz, Ph.D., designed the recording system.

calculated it exactly by measuring the relation of the height of one wave of the damped vibration to that of the next wave of similar direction. After the frequency had been elevated the relative height of the second wave diminished to about one third of that present during the classic Dock procedure.

In Figs. 1, 2 and 3 one can compare typical examples of classic shin bar records

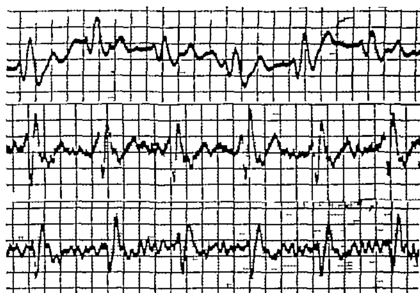
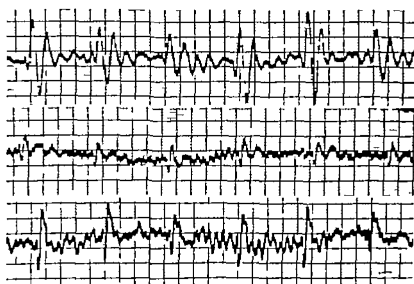


Fig. 1. R[illegible]rd of a normal 28 year-old subject. *Top*, Classic Dock record. *Center*, HF shin bar record. *Bottom*, ULF force record. Note the similarity between the last two and the improvement of the HF shin bar record over the shin bar record secured by the usual technique.



F[illegible] Normal 2[illegible] year-old subject. *Top*, Classic Dock record. Note deep [illegible] waves and [illegible] waves. *Center*, HF shin bar record. Note great diminution of [illegible] and [illegible] waves and close resemblance to contour of ULF force record (*bottom*). The difference in amplitude is due to differences in amplification.

improved HF shin bar records and ULF force records secured in our healthy subjects. The improvement of the HF shin bar record over those secured at the lower frequency is always considerable and sometimes, as in Fig. 3, very great indeed, the contour being completely changed.

Fig. 4 permits a comparison between HF shin bar records and ULF force records in 6 other subjects, some with normal, some with abnormal records. Obviously the resemblance is very close, as it is in all our 44 subjects. But the records chosen also show the differences, the much greater effect of respiration on the HF shin bar record and the larger amount of high frequency information, that is, the greater number of notches, in the ULF force record.

Discussion

The reason that the physical changes caused by tightening the subject to his surroundings should have such a beneficial effect on the shin bar record will be manifest to mathematically minded readers from Noordergraaf's analysis. Moreover, the success of the method depends on the employment of the nonlinear properties of the dorsal tissues to raise the frequency. We hope that the following analogy will make the matter clearer to those without special mathematical training.

The principles concerned are the same as those which govern the movement of a child in a swing. To make the child swing back and forth, one delivers a push at regular intervals. If this push is delivered at the proper point in the swing cycle so that the movement of the swing is reinforced, the two frequencies are in resonance, and little effort is required to make the child swing high; but if delivered at a time when the movement of the swing was opposed to the direction of the push, the same push would have a very different effect on the child's swinging. In other words, one has great difficulty in estimating the strength of the push (force) from the height of the swing (the aim of the shin bar ballistocardiograph), for differences in the time relations introduce very serious errors, warping the relation between the movements observed and the forces which originate them.

Similarly, the two main forces of each heartbeat, delivered first footward and then headward, set the body swinging back and forth on its supports. We observe the swing by taking shin bar ballistocardiograms, but

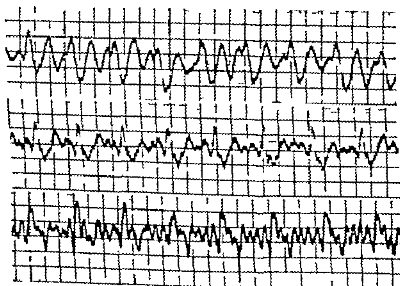


Fig. 3. Subject n. ... weight (213 p... 5 feet 7 inches tall). Top, Classic Dock record. Note very small H, I, and J waves and distortion by resonance in record. Center, HF shin bar record; note the great improvement and close resemblance to ULF force record (bottom).

Table I Frequency of the body movement on the floor before and after tightening it by the technique described

Subject	Before tightening		After tightening	
	Dock system with roller under heels (1)	Dock modified with heels on floor (2)	HF shin bar with heels against wall (3)	Difference (3) − (1)
	cycles per second			
K T	3 9	5 0	7 1	3 2
I S	3 8	5 0	12 3	8 7
R H	5 0	6 0	10 0	5 0
F H	3 4	4 1	8 3	4 9
C F	5 0	5 0	8 3	3 3
W J	—	6 3	11 0	—
D W	3 5	5 0	11 0	7 5
R G	3 5	5 0	8 3	4 8
G N	4 5	6 3	8 3	3 8
Z F	3 5	6 3	8 3	4 8
P N	3 5	4 8	8 3	4 8
C N	3 8	5 0	10 0	6 2
I D	3 8	5 0	8 3	4 5
L N	4 1	6 0	10 0	5 9
N I	3 5	4 1	8 0	4 5
M R	4 1	5 0	10 0	5 9
T R	4 1	5 0	10 0	5 9
H F	4 1	5 0	8 3	4 2
R C	4 1	5 0	10 0	5 9
K R	3 5	5 0	8 3	4 8
Mean	3 9	5 2	9 2	5 2
σ	0 47	0 63	1 49	1 31

N rk nd at pa ts 8 u rmal subjects

the time relation between these forces of the circulation and the swing frequency is not known to us Thus when a shin bar record of body movements is unusually small or distorted this might indeed be due to the fact that the forces of the circulation were abnormally small or were delivered in an abnormal manner but the finding might also be due to changes in the usual time relations between the forces and the swinging body or to a difference in body properties as well as to cardiac abnormality

This difficulty reaches a maximum when the frequency of the body swinging on its support and that of the forces which set it going are nearly the same as is true when most persons lie on a rigid surface The more different these two rhythms the less the difficulty becomes By a simple method we have doubled the frequency of the body on its supports making it very different from the rhythm of the forces As a result the error largely disappears and shin bar records now closely resemble true records of circulatory forces secured by elaborate apparatus designed to eliminate altogether the error due to the physical properties of the body

Despite the close resemblance between HF shin bar records and ULF force records the two are not identical Respiratory arching of the base line is more prominent in HF shin bar records and they do not contain the small notches which are so often seen in ULF force records These

differences are to be expected from Noordergraaf's theory[3] since high frequency information in the HF shin bar method is sharply attenuated. If this proves to be a disadvantage for clinical use, it is one shared by HF tables.[7]

Occasionally we see small differences between HF shin bar records and ULF records that we do not fully understand. The chief of these is a rounded headward L or N wave which occurs in early diastole in perhaps one tenth of our HF shin bar records, and which has no counterpart in the ULF records of those subjects. This difference occurs when the correspondence between the major systolic waves is good.

However, in one important respect these improved shin bar records are still inferior to records from either ULF or HF tables. When one attempts to calibrate the HF shin bar method by a known force, footward in direction, placed against the subject's head, the expected deflection of the record's base line results. The amplitude of this deflection can be easily measured and compared with the amplitude of the recorded ballistocardiogram. But unhappily, quantitative study shows that

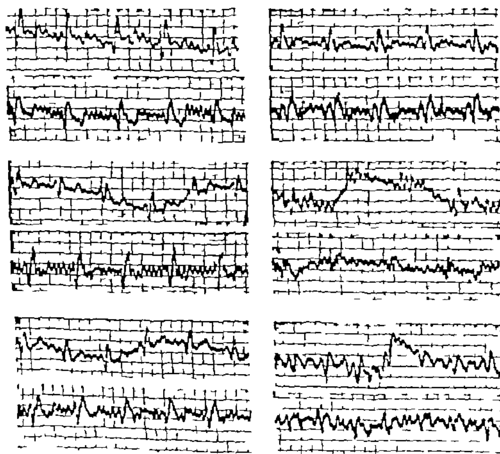


Fig. 4. Comparison between HF shin bar records and ULF force record in 3 healthy subjects and 3 patients with heart disease. *Left*, Normal subject. *Right*, Patients. The HF shin bar record is above the ULF record in each instance. In the right hand column, the upper pair of records was taken 1 month after cardiac infarction in a 40-year-old patient. Note fine recovery of both records. The middle pair was taken 1 year after a cardiac infarct in a 58 year-old man; the wandering of the base line in the HF shin bar record is due to respiration. Note marked splitting of waves in both records. The lower pair was taken in a 23 year-old man with a slight fever in whom pericarditis had been diagnosed. Note that, despite the general resemblance, the J waves are notched in the ULF record but not in the HF shin bar record. The large upward deflection in the HF shin bar record is a respiratory artifact.

an estimate of the force content of HF shin bar records made by such a calibration is several times larger than the corresponding values obtained in force records of the same subjects lying on either a ULF or an HF table. Evidently the body is elastic and when a known force is applied to the head of a reclining subject the body behaves much as a helical steel spring would do, the displacement caused by a force applied to the free end diminishing as the fixed end is approached. Thus a simple method of calibrating HF shin bar records comparable in accuracy to those available for either ULF or HF table records has not been attained.

Two other difficulties, although of minor importance, must be mentioned. Some patients, when tightened so that their body support frequency attains 12 cycles per second or more, have developed a muscular tremor which ruined the record. Our best records have been secured at a frequency of from 8 to 12 cycles per second. Also, our HF shin bar records are more subject to trouble from vibrations of the building than are classic Dock records, since our subjects are much more tightly attached to the building than in the original technique.

In Dock's original shin bar method the body movement was so large that records could be secured by a simple electrical pickup without amplification, but the more the subject is tightened the more the movements of the body in space are reduced, so that amplification is required in our HF shin bar method. But amplification presents few difficulties today, and the smaller movement of the body in space may well be an advantage, since the body is shaken less and there is less danger that loose parts set into vibration will produce forces which distort the record.

In taking HF shin bar records there is always the danger that the necessary body tightness may not be attained or, if attained, may be lost because the feet lose contact with the wall without the operator becoming aware of it. To protect ourselves against this possibility, we have made it a rule to put a test for body frequency at the end of every record. The fact that the frequency was sufficiently high demonstrates conclusively that body tightness was adequate while the record was being taken.

When comparison is made with records secured by the classic shin bar method, our results show clearly that the gain in accuracy secured by the new technique is very great, and that the loss in convenience is minor. For neither of these simple methods have we at present a satisfactory method of calibration such as is available for ULF and HF tables.

When compared with the ULF force record, the HF shin bar record lacks the high frequency components of the former. If the notches which are so common in ULF force records secured in healthy subjects carry important clinical information, the ULF method will be found to be far superior, but we have no present knowledge that this is true. When one seeks to judge cardiac abnormality by the absence or great diminution of waves normally present, and by their gross distortion, our evidence indicates that the HF shin bar method would be little, if at all, inferior to the ULF method, and certainly the simplicity of the new procedure would make it available to many doctors who will never possess a ballistocardiographic table. Certainly by this simple technique the large deviations of contour from the normal are clearly shown.

Finally, our results provide conclusive evidence of the correctness of Noordergraaf's analysis of the difficulties of the classic shin bar method. By employment of the means he suggested, this method is very greatly improved. Indeed, after improvements suggested by increased understanding, the force records secured by all of the three types of ballistocardiograms—ULF, HF, and HF shin bar—are very similar indeed.

Summary

Greatly improved shin bar ballistocardiograms can be secured by a simple technique in which the frequency of the movement of a body on its supports is increased. These high frequency shin bar records closely resemble ultralow frequency force ballistocardiograms, although the two are not identical in certain respects.

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Capacitance-plethysmograph method for separating blood flow in muscle and skin in the human forearm

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Plethysmography is an excellent method for estimating total blood flow in segments of the human extremity;[1] however, its usefulness is frequently limited by the difficulties involved in separation of flow through skin and muscle. Several approaches have been devised which provide a semiquantitative separation, but none is completely satisfactory. Iontophoresis of Adrenalin into the skin of the segment may be used to shut down the cutaneous flow, but it is acceptable only when a critical amount of catecholamine has penetrated; the proponents of this technique are aware that critics imply that this level may have minimal central effects. Estimation of the oxygen saturation of venous blood draining superficial and deep tissues of the forearm[2] offers only a rough qualitative estimate of flow in the two types of tissue and presupposes a relatively constant extraction of oxygen by the tissues. The use of the flow rates in the finger tip as an index of the flow in the skin of the forearm segment is no longer tenable in view of the divergent physiologic responses of circulation in these areas.[3] Finally, the heat flow needle of Hensel[4] and the tissue clearance method of Kety,[5] which do measure some function of the blood flow in the tissues separately, are not satisfactory because their exact significance is still unclear. Obviously, an alternative, more direct technique is needed.

Use of the electro-capacitance plethysmograph[6] in conjunction with local counterpressurization of the segment makes possible the direct, simple, nontraumatic estimation of the distribution of blood flow between skin and deeper tissues. This experimental procedure and its physiologic validation are presented below.

Rationale

Hyman and associates[7] reported a decrease in the apparent blood flow in the forearm when measured by the segmental plethysmograph technique[8] at increased counterpressure; as pressures rose above 10 mm. Hg, apparent blood flows progressively decreased. These differences could be explained if the flow of blood through part of the segment of forearm tissue was impeded. The alternative possibility that some systematic inherent error in the

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Fig 1 Arrangement of pneumatic cuff and electro-capacitance plethysmograph for application of counterpressure during determinations of blood flow. The calibration cuff connects to a system which introduces exactly 1 ml of saline into the balloon this raises the electrolytic surface beneath capacitance plethysmograph by an amount equivalent to a 1 ml increment in volume in the forearm

segmental plethysmograph determinations at elevated pressures might explain the data was discarded on the basis of the following experiment. A special pneumatic cuff was wrapped around the forearm segment directly beneath the screens of the capacitance plethysmograph as illustrated in Fig 1. With this arrangement it was possible to make measurements of blood flow with the capacitance plethysmograph during the application of graded counter pressures in the pneumatic cuff. A typical curve relating apparent blood flow (as measured with the capacitance plethysmograph) to local counterpressure is shown in Fig 2. Blood flow decreased progressively as counterpressure increased from 5 to about 25 mm Hg. Between 25 and 35 mm Hg the blood flow remained almost constant; at pressures above 35 mm Hg the apparent blood flow again decreased with increasing pressure. Such a plateau has been obtained in every case thus far examined—usually between 22 and 35 mm Hg of counterpressure. Since the pressure in the capillaries of the skin is of this magnitude it seems likely that the plateau represents cessation of cutaneous circulation; a higher critical value must be reached before blood flow in muscle is compromised. A plethysmograph that imposes no counterpressure measures blood flow through *all* of the tissues of the forearm whereas at a critical counterpressure only the blood flow through deeper muscle tissue is measured.

The effect of counterpressure on blood flow through skin and muscle was checked by measurements of tissue clearance with and without counterpressurization.

This method was validated by measuring total and muscle blood flow in the forearm when circulation through skin or muscle was individually altered by appropriate physiologic stimuli. Reflex heating in a quiet and cool environment was used to increase the flow of blood through only the *skin* of the forearm; the flow of blood through *muscle* only was increased by local exercise and measured during the period of postcontraction hyperemia.

The details of the experiment are set forth in the following section along with the results. In all cases the findings agree with the hypothesis established above.

Experimental

A. Measurements of tissue clearance. In 9 subjects tissue clearance was determined by the usual method. About 0.04 ml of saline containing up to 0.5 microcuries of Na was injected either intradermally or at a depth of about 1 cm

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Fig 2 The effect of counterpressure on apparent blood flow in the forearm as measured with the electro-capacitance plethysmograph. *Ordinate* Apparent blood flow expressed in milliliters of flow per 100 ml of tissue per minute. *Abscissa* Counter pressure applied in the pneumatic cuff directly beneath the capacitance plethysmograph. Note the marked flattening of the curve in the pressure range of 27 to 27 mm Hg

Table 1 Postcontraction hyperemia

Subject	Control			Excess		
	5† (ml/100 ml arm/min)	35 (ml/100 ml arm/min)	5-35 (ml/100 ml arm/min)	5 (ml/100 ml arm)	35 (ml/100 ml arm)	R 5/35
Clem	9 30	4 10	5 20	29 70	28 70	1 040
White	2 20	0 77	1 43	10 00	8 30	1 210
Fielding	2 80	1 62	1 18	16 20	13 80	1 170
Greeson	1 50	0 57	0 93	24 70	17 70	1 400
Kinkead	2 36	1 53	0 83	15 10	15 90	0 950
Kinkead	5 17	3 03	2 14	7 81	6 45	1 210
Average	3 89 ± 1 09‡	1 94 ± 0 51	1 95 ± 0 06	17 25	15 14	1 160 ± 0 140

F[illegible] blood flow was calculated [illegible] the following manner. All of the arterial blood flow values at the given counterpressures were [illegible] and the them was [illegible] divided by the base line. The postcontraction flow measurements [illegible] were larger than the [illegible] total [illegible] were the [illegible] to provide the total blood [illegible] the postcontraction hyperemia period. From this total we [illegible] the blood flow that would have [illegible] the product of the blood flow in the elapsed time. The excess blood flow was the difference between the actual postcontraction flow and the [illegible] basal flow during an equal period of time.

†C[illegible] in ml per [illegible]

‡Standard error of the mean

into the skeletal muscle of the forearm. Activity remaining at the site of injection was followed by a scintillation detector coupled to a pulse height analyzer and count rate meter. Immediately after each injection a pneumatic cuff (6.5 cm wide) was placed on the arm with the site of injection midway between its two edges. The isotope activity was followed for 4 minutes while the pressure in the cuff was minimal, then for 4 minutes after the pressure in the cuff had been elevated to 35 mm Hg, and finally for 4 minutes after the pressure had been restored to the minimal level. A final count to be used as a background value was obtained no less than 30 minutes after the initial injection. Fig. 3 is a plot of the results obtained in a typical experiment. The application of counterpressure decreased clearance from the superficial site of injection to one third of the control value but had only a negligible effect on clearance from muscle.

B. Reflex heating. The effect of reflex heating was determined on 6 subjects according to the following protocol: each subject was placed in a room at 18 C for about 15 minutes. Blood flow in the forearm was then determined by venous occlusion with the capacitance plethysmograph, the hand was isolated by arterial occlusion at the wrist. When measurements indicated a stable basal blood flow, the subject was heated by means of an electric blanket. A second series of measurements of blood flow was made when his oral temperature had increased

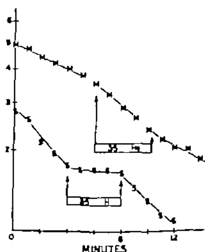


Fig. 3 Clearance of Na[22] from sites of injection in the forearm before, during, and after application of local counterpressure. *Ordinate:* Radioactivity remaining at injection site (log scale). *Abscissa:* Time in minutes. *Curve M:* After an intramuscular injection. *Curve S:* After an intradermal injection. During the indicated interval the counterpressure cuff was inflated to 35 mm Hg.

by 0.5 to 1.0°F. After a period of recovery the test was repeated exactly as in the first case except with 35 mm Hg of counterpressure in the cuff below the capacitance screens. In a typical experiment shown in Fig. 4 the increase in counterpressure to 35 mm Hg had only a small effect on the flow rate in subjects at control temperatures but during reflex heating the same counterpressure eliminated entirely the increase in flow noted without counterpressure.

If flows measured at the low and high pressures may be taken to represent the total and muscle circulation respectively then the difference between them should equal flow in the skin. Calculations based on these assumptions indicate a threefold increase in blood flow in the skin during reflex heating. Accepting a value of 8.6 ml skin per 100 ml forearm[10] the calculated blood flow through skin increases from about 22 to about 62 ml per 100 ml of skin per minute. Increase in blood flow through the muscle averaged only 5 per cent.

C. Postcontraction hyperemia. In 6 experiments on 5 subjects postcontraction hyperemia was compared at two levels of counterpressurization. The subjects were studied in a comfortably warm room; the electrocapacitance plethysmograph and the counterpressurization cuff were applied as described above. After the basal rate of blood flow was determined with minimal counterpressurization the subject clenched and opened his fist at 1 second intervals for 1 minute. Immediately thereafter measurements of blood flow in the forearm were made at frequent intervals (15 to 30 seconds) until the values returned to the control level. After a period of recovery basal values were obtained and the experiment was repeated at a counterpressure in the previously determined plateau range. The total and muscle flows and the differences between them (skin flow) obtained in such an experiment are plotted in Fig. 5. The curves for the two different levels of counterpressure are parallel; hence the difference curve does not deviate significantly from the basal values. The data summarized in Table I show reasonably good agreement between the excess flow during postcontraction hyperemia measured at low and that measured at high counterpressures.

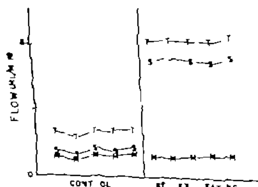


Fig. 4. Effect of reflex heating on blood flow in the forearm. *Ordinate*: Measured blood flow in milliliters per 100 ml per minute. *Abscissa*: Time. *(I) left*: Control state. *(II) right*: After body temperature had been increased. *Curve T*: Total blood flow measured without counterpressure. *Curve M*: Blood flow measured [illegible] counterpressure in the plateau range (equivalent to blood flow in muscle). *Curve* [illegible]: Difference between [illegible] counterpressure curves [illegible] reflex heating [illegible] of the [illegible] the change in total flow can be explained in terms of a [illegible] flow.

Discussion

The results obtained in the experiments described above are all consistent with the hypothesis that an appropriate local counterpressure can eliminate the flow of blood through the superficial tissues without seriously embarrassing flow in the deeper structures. Results of the studies on tissue clearance although not conclusive strongly suggest that counterpressure never seriously modified the flow of blood 1.0 cm below the surface of the forearm but these plateau value pressures always decreased clearance from the sites of injection in the skin. Tissue clearance does not necessarily parallel total blood flow since the arteriovenous anastomotic shunts or bypass vessels may still be open but the marked qualitative difference in the effect of counterpressure at the two levels must be indicative of differential responses of the circulation at these levels.

That the pressures chosen were in the

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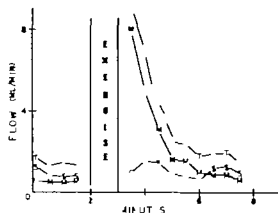


Fig 5 Postcontraction hyperemia *Ord male* Flow in milliliters per 100 ml of forearm tissue per minute *Abscissa* Time in minute Left of the *Exercise* section are basal values for calculation Values for postcontraction hyperemia are shown to the right of the exercise section Other symbols as in Fig 4

general range required to modify flow in the skin is supported by Lewis demonstration that local application of such pressures can modify blood flow to evoke a subsequent cutaneous reactive hyperemia Direct[13] and indirect[14] measurements of the pressure at the arteriolar end of cutaneous capillaries give pressures averaging 32 mm Hg so that flow in the skin should be stopped by the application of a local counterpressure of this amount the blood which would ordinarily flow through this tissue is diverted via collaterals to the deeper parts

Data relative to the control state are compared with similar figures reported by Cooper and co workers[19] in Fig 6 Although the slopes of both regression lines are similar the line for our data projects to intercept the total blood flow axis below 0 5 ml per 100 ml arm per minute considerably closer to the origin than the intercept implied by Cooper and associates Our estimates of blood flow in the skin exceed those obtained by iontophoresis by a constant increment of about 1 ml This may represent a fault of either method From data on loss of temperature and absorption of helium reported by workers in other laboratories Cooper and associates[19] calculated forearm skin blood flow to be between 1 2 and 1 5 ml per 100 ml arm per minute In our studies values range from 0 8 to over 5 0 ml per minute with more than half of the cases between 1 and 2 ml per minute in the cases reported by Cooper and associates the most frequent values were below 1 ml per 100 ml forearm per minute This agreement with independent estimates and the closer approach of the intercept to the origin seem to favor the new technique If the counterpressures used intrude on some small fraction of the blood flow in the muscle of the segment our technique would tend to overestimate the blood flow in the skin However the great variability in the relationship between blood flow in skin and total flow even in the control state rules out precise comparisons

The influence of counterpressure on blood flow through the tissues of the forearm has been studied by at least three other groups Dornhorst and Whelan[15] compared a minimal pressure and one chosen to reduce the effective local blood pressure by about 50 mm Hg Blood flows were consistently diminished by the

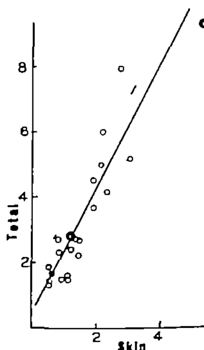


Fig 6 Relation between measured total blood flow and calculated blood flow through the skin *Ord male* Total blood flow in milliliters per 100 ml of forearm per minute The points and the solid regression line represent data obtained in the present study The broken regression line is taken from the report of Cooper and associates[19]

counterpressure but the data presented do not permit evaluation of the change. Burton and Yamada[16] and Ashton[17] studied the blood flow at various counterpressures and both express their results in terms of effective transmural arterial pressure. The data presented by the first authors in a composite graph cannot be directly related to the counterpressure flow curves reported in the present study. In Dr. Ashton's study, Figures 1 and 2 suggest a plateau of the sort reported here. In Figure 1 the slope of the forearm flow versus pressure is decreased in a range corresponding to counterpressure between 20 and 50 mm. Hg. The analogous curve for data on the calf indicates a flattening in a counterpressurization range of approximately 40 and 60 mm. Hg. This higher level of pressure may be required to modify the flow of blood in the skin of the larger segment.

Burton and Yamada[16] first suggested that reduced transmural pressure diminished flow because of an instability of small blood vessels which results in their closure. The results of the present study do not deny this possibility, but it must now include the shut down of circulation in the superficial tissues at pressures which do not influence the deeper tissues. The plethysmograph used by Burton and Yamada was considerably longer (16 cm.) than the counterpressurization cuff (6.5 cm.) used in the present study; minimal pressures applied over a longer segment of forearm may be transmitted to deeper tissues from the broader base.

When the flow of blood through skin and muscle was independently modified, the resulting measurements confirmed our predictions. Elevation of body temperature to a level which ordinarily increases blood flow in the forearm gave data which imply that the increase was confined entirely to the component that we consider to be the skin. This fraction of the blood flow increased by an average of 180 per cent, whereas the flow of blood through the muscle component increased by less than 5 per cent. This agrees quite well with the results reported by Cooper and associates.[9] Burton and Yamada[16] reported data which indicate that in reflex vasodilated subjects a greater increase in flow results when counterpressure is minimal than when counterpressurization is increased. Their data, unlike ours, suggest some reflex-induced increase in flow at all counterpressures used, but the scatter of their points and the way in which the data are related make direct comparisons difficult.

The results with the postcontraction hyperemia were as anticipated and correspond almost exactly to the findings of Dornhorst and Whelan.[18] The identical excess flow of blood, i.e., the increments above the basal values, when measured at low and high counterpressures indicates that the moderate local muscular contraction does not modify the flow of blood in the overlying skin and confirms earlier studies.[1-3] Since our data were obtained on two successive bouts of exercise assumed to be of the same magnitude and to evoke exactly the same response, their apparent variability is greater than actual. More consistent data would be obtained if the blood flows were determined simultaneously by a double plethysmograph system over the same group of muscles. A modification of our current technique to permit such a measurement is currently under way.

Summary

We offer a method to separate blood flow in skin from that in muscle using an electro-capacitance plethysmograph for measurements of flow and a pneumatic counterpressurization cuff underlying the electro-capacitance screen. By inflating the pneumatic system to carefully controlled pressures, it is possible to obliterate the flow of blood in the skin without modifying that in muscle. The argument was validated by experiments in which such counterpressurization was shown to have little or no influence on the clearance of locally injected isotope from muscle underlying the counterpressurization cuff, whereas it did diminish to less than one third the clearance of intradermally injected isotope. When blood flow in skin alone was augmented by means of reflex heating, plethysmographic measurements showed an increase in *total* blood flow but no modification in the blood flow with

counterpressurization Increased local muscle blood flow by exercise of a small group of forearm muscles produced equal increases in both total flow and flow measured after the application of the counter pressure

The relationship of these findings to earlier measurements of blood flow in the human forearm under conditions of increased local counterpressure is discussed There is no contradiction between our findings and those previously reported We propose that this new technique offers a significant improvement over the currently available techniques for the separation of blood flow in muscle from that in skin in the human forearm

We should like to thank Miss Kathryn Ballard who is responsible for the drawing Dr Rita Paldino who calculated the statistical parameters reported and the regression curve in Figure 6 and Mr Patricia Fielding for the secretarial work and bibliographic searchings We also thank the subjects who participated in the measurements reported

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The effects of chronic impairment of cardiac lymph flow on myocardial reactions after coronary artery ligation in dogs

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Louis N. Katz, M.D.
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Chronic impairment of lymph flow leads to fibrosis in the affected part.[1] Chronic impairment of cardiac lymph flow in the dog results in ventricular endocardial fibroelastosis.[2] Furthermore, scar formation after injection of autologous blood into the wall of the left ventricle is increased in dogs with chronic impairment of cardiac lymph flow.[4]

The present study, an extension from previous observations, was undertaken to determine the effects of interference with cardiac lymph drainage upon the myocardial healing processes after coronary artery occlusion. The reactions around the silk ligature used to produce the coronary occlusion also will be described in some detail.

Methods

Dogs were anesthetized with sodium pentobarbital (30 mg. per kilogram). By means of an aseptic technique an incision was made in the left side of the thorax in the third intercostal space. The heart was exposed and the pericardium was incised parallel to the phrenic nerve. A small amount of T-1824 dye (approximately 0.2 ml.) was then injected through a 27 gauge needle into the left ventricular myocardium in order to visualize the mediastinal lymphatic system draining the heart.[5] The visualized mediastinal cardiac lymphatic system was then resected by the method previously reported.[2]

After the lymphatic resection, the third small branch of the anterior descending coronary artery distal to the perforating branch (running toward the lateral wall of the left ventricle) was ligated at its origin with black silk. The needle was passed through the epicardium and superficial myocardium so that the small veins on either side of the artery were also ligated. The pericardium was left open in all dogs after operation.

Control dogs with the cardiac lymphatic system left intact were submitted to comparable ligations of a coronary artery branch.

With the technical assistance of [illegible] and [illegible] Gerry.
From the Cardiovascular Institute [illegible] the Department of Pathology, Michael Reese Hospital and Medical Center, Chicago, Ill.
This study was aided by Grant [illegible] from the Chicago Heart Association and Grant [illegible] from the National Heart Institute.
Received for publication [illegible] 30, 1963.
[illegible] Pathology, supported by Grant [illegible] from the [illegible] Public Health Service. [illegible] Department of Pathology, University of Illinois College of Medicine, Chicago, Ill.
**Established [illegible] of the American Heart Association, supported by the Chicago and Illinois Heart Association.

Thirty five dogs (22 with cardiac lymphatic obstruction and 13 controls) were successfully operated on. Fourteen of the 35 animals (10 with cardiac lymphatic obstruction and 4 controls) died within 1 week after operation. All of the remaining dogs except 2 control animals which died spontaneously were killed at varying time intervals up to 72 days postoperatively. All sacrificed dogs were reoperated upon prior to death in order to assess the status of the mediastinal cardiac lymphatic system after injection of T 1824 dye into the ventricular myocardium.[3]

Postmortem examinations were performed on all dogs. The sites of the coronary artery ligature and the myocardial infarction were sectioned serially. Sections were treated with hematoxylin and eosin and combined orcein Verhoeff-Gieson stains.

Results

Myocardial infarction. The myocardial infarctions produced were quite irregular in shape and therefore exact measurements could not be made. However, the greatest diameters in three dimensions were measured to calculate the approximate volumes of the myocardial scars in the two groups of animals which died 5 days or more after operation.

Fig. 1 shows the approximate size of the scars in relation to the duration of postinfarction survival in the two groups of dogs. In general, the myocardial infarcts were larger in the dogs with chronic impairment of cardiac lymph flow; this difference became more noticeable with the passage of time.*

A. CONTROL DOGS (with unimpaired cardiac lymph flow). Those dogs which died within 3 days after operation showed areas of acute necrosis of the myocardium extending into the anterior papillary muscle of the left ventricle with numerous polymorphonuclear leukocytes (PMN's) present.

One week postoperatively the infarct was smaller and more circumscribed, involving mainly the deep muscle bundle and the proximal portion of the papillary muscle. The necrotic areas were replaced primarily by loose granulation tissue with numerous fibroblasts, macrophages and a few Anitschkow cells. Isolated necrotic heavily calcified muscle fibers were also noted.

In dogs which survived for longer periods of time the myocardial infarction generally became smaller. Two weeks postoperatively the infarcted area was almost completely replaced by organizing granulation

*When the mean [illegible] of the [illegible] the two groups of dogs [illegible] impaired [illegible] was found that [illegible] 0.96 [illegible] ± 0.1 [illegible] 1.70 cm ± 0.34 [illegible] and [illegible] lymph obstruction the difference [illegible] When [illegible] after 30 days [illegible] compared [illegible] 0.55 ± 0.21 [illegible] 1.26 ± 0.29 [illegible] cardiac lymph obstruction [illegible] but the differences [illegible] (because of the small number of dogs used).

Fig. 1. Bargraph comparing scar size (cm³) over time (days) after ligation of a coronary artery branch in control (without lymph obstruction) (*white bars*) and in dogs with cardiac lymphatic obstruction (*shaded bars*).

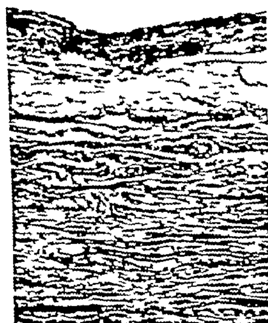


Fig 1 Co trol dog 2 d after or ary rtery branch l gation Not that the infarct composed of dense scar tis ue and that the e is a thin trip of normal myocardium between the sl ghtly thickened endocardium and the nfar t Or ein an Gie son X150

definite gross infarction extending into the anterior papillary muscle By 3 days after operation much fibrin had been deposited between the necrotic muscle fibers and dilated thin walled channels considered to be lymphatic vessels were noted throughout this are

One week postoperatively a large tan yellow infarct involved almost the entire anterior papillary muscle and adjacent myocardium At this time the histology was similar to that in the controls Two weeks after operation a moderately large infarct larger than that in the control dogs and extending in some areas the entire thickness of the myocardium was present Histologically a large central area of acute necrosis was surrounded by organizing granulation tissue which extended into the area of acute necrosis

The gross size of the infarct in dogs which survived more than ? weeks post operatively generally became progressively smaller with time until the latter part of the experiment when there was some increase in size However the zone of infarc

tissue and many connective tissue fibrils were flanked by numerous fibroblasts Calcified necrotic muscle fibers were still present

Three weeks after coronary artery ligation the area of infarction was composed mainly of a central core of dense fibrous tissue surrounded by granulation tissue After 4 weeks fibrous tissue predominated and the only remnant of infarction 72 days postoperatively was dense scar tissue that contained a few chronic inflammatory cells (Fig 2A)

In the control do s the endocardium underlying the myocardial infarction showed occasional focal fibroblastic and elastic tissue proliferation In almost all of the control dogs a thin strip of normal muscle was present between the area of myocardial infarction and the endocardium (Fig 2A)

B DOGS WITH IMPAIRMENT OF CARDIAC LYMPH DRAINAGE Early coagulation necrosis was present in the deep subendocardial myocardium within 24 hours after operation and by 48 hours there was

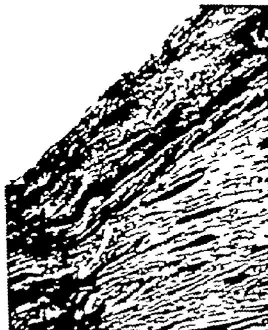


Fig B Dog w th l mphatic obstruction 48 days after l g t of o ta art y br nch Note the m dial scar extending to the markedly thickened endoca d um Or ein an G eson X150

Thirty-five dogs (22 with cardiac lymphatic obstruction and 13 controls) were successfully operated on. Fourteen of the 35 animals (10 with cardiac lymphatic obstruction and 4 controls) died within 1 week after operation. All of the remaining dogs, except 2 control animals which died spontaneously, were killed at varying time intervals up to 72 days postoperatively. All sacrificed dogs were reoperated upon prior to death in order to assess the status of the mediastinal cardiac lymphatic system after injection of T-1824 dye into the ventricular myocardium.[5]

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* [illegible] 0.96 ml ± 0.12 [illegible] and 1.0 ml ± 0.34 [illegible] 10 days [illegible] found 0.58 ± 0.21 [illegible] and 1.26 ± 0.39 [illegible] (particularly) but the [illegible]

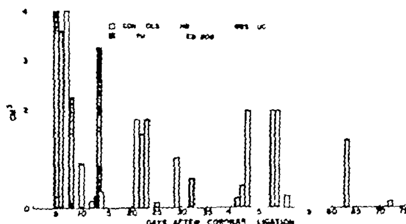


Fig. 1. Bar graph comparing scar size (cm.³) over time (days) after ligation of coronary artery branch in control (without lymph obstruction) (white bars) and in dogs with cardiac lymphatic obstruction (shaded bars).



Fig 4B Control dog 25 days after ligation of coronary artery branch Note the well vascularized fibrous tissue (at top of photo) replacing the myocardium subjacent to the ligature Gomori an Gieson X60

in the region of the ligature In 6 of these dogs a granulomatous reaction around the ligature formed a firm white nodule (usually approximately 0.5 cm in diameter) Cross sections through these nodules revealed the ligature material embedded within a wedge shaped fibrotic area which extended into the adjacent myocardium

In the dogs killed 7 to 9 days after operation a meshwork of early organizing granulation tissue extended from around the ligature into the subjacent necrotic myocardium Small numbers of atrophic muscle fibers that contained considerable calcium were present at the edge of the granulation tissue Fibrin persisted in several large foci enmeshing large numbers of inflammatory cells

Two weeks postoperatively a well circumscribed fibroblastic reaction was seen around the ligature itself (Fig 4A) Macrophages and giant cells were noted The adjacent epicardium was edematous and infiltrated with small numbers of chronic inflammatory cells The subjacent myocardium was replaced by moderately dense granulation tissue with foreign body giant cells surrounding several isolated necrotic heavily calcified muscle fibers

Twenty five days postoperatively the granuloma consisted of many PMNs infiltrating the suture material surrounded by fibroblasts and large histiocytes The superficial myocardium was replaced by dense connective tissue (Fig 4B) Numerous thin connective tissue fibrils extended through the granuloma

From 29 to 72 days after coronary ligation the reaction around the suture material remained essentially unchanged except for an increasing amount of fibrous connective tissue The epicardium adjacent to the suture reaction appeared to be normal The subjacent myocardium was replaced by dense scar tissue

B DOGS WITH IMPAIRMENT OF CARDIAC LYMPH FLOW The reactions around the ligatures were more marked than in the



Fig 4C Dog with lymph obstruction 8 days after ligation of coronary artery branch Note the early granulomatous proliferation of tissue heaping up around the suture and the wedge shaped area of acute myocardial infarct with extensive calcification in the adjacent myocardium Hematoxylin eosin X12.5

control animals at comparable times An early acute coagulation necrosis of the subjacent myocardium was noted as soon as several hours after the coronary artery ligation A large area of epicardium around the ligature was involved with considerable deposition of fibrin on the surface marked edema and focal infiltration with PMNs and numerous dilated thin walled channels

Two to 3 days after operation the thickened epicardium was almost completely replaced by PMNs and necrotic debris

By 1 week postoperatively a heaping up of tissue over the ligature was noted (Fig 4C) In the following weeks a large firm tan white mass developed which surrounded the suture material and extended into the subjacent myocardium The large tumor formation persisted in dogs which survived for longer periods of time and at 7 weeks postoperatively measured up to 1 2 cm in greatest diameter (Fig 4D)

Histologic sections of this mass 1 week after operation revealed a foreign body granuloma which consisted mainly of PMNs and histiocytes immediately encasing the suture material and surrounded by fibroblastic tissue with many foreign body giant cells

From 2 to 6 weeks postoperatively the findings around the ligature were similar to those in the control dogs except for a greater fibroblastic reaction For variable distances on all sides of the suture the epicardium was involved with a similar granulomatous reaction (Fig 4E) In those dogs which survived for longer periods of time the granuloma continued to become larger Numerous PMNs reappeared at 6 weeks and were especially prominent in large sheets throughout the lesion at 7 weeks after operation (Fig 5A)

At the end of the experiment (63 days postoperatively) the reaction around the ligature remained large and cellular A few giant cells were present Histiocytes predominated with lesser numbers of fibroblasts lymphocytes and PMNs



Fig 4E Dog with lymphatic obstruction 21 days after ligation of coronary artery branch Note formation of granuloma in epicardium some distance from the site of ligature Hematoxylin and eosin ×150



Fig 4D Dog with lymphatic obstruction 21 days after ligation of coronary artery branch Note the large nodule formed at the site of ligature which is composed of dense fibroblastic tissue Hematoxylin and eosin ×12 5



Fig. 5A. Dog with lymphatic obstruction 48 days after ligation of coronary artery branch. Note the marked infiltration of polymorphonuclear leukocytes into the suture granuloma. Hematoxylin and eosin. ×235

in the dogs with lymphatic obstruction, especially in the case of older infarcts. Although microscopically the usual process of necrosis followed by granulation tissue repair and ultimate fibrosis was noted in both groups, large areas of recent necrosis surrounding older infarcts were seen only in dogs with lymphatic obstruction. This change was especially prominent in animals which survived 42 days or longer postoperatively and may account for the apparent increase in size of the infarcts noted in the dogs with cardiac lymphatic obstruction at this time. It coincided with a marked increase in PMNs in and around the coronary artery ligature (see below). Calcified atrophic muscle fibers were also more prominent in the infarcts in the animals with lymphatic obstruction. These deviations from the expected healing pattern appear to be related to the impairment of cardiac lymph flow and may result from persistent local edema and delayed removal of necrotic debris and inflammatory cells. The possibility that the recent necrosis around the area of infarction is

Dense connective tissue almost completely surrounded the area. Many dilated thin-walled vessels were present throughout the older lesions (Fig. 5B).

Discussion

The mammalian heart has an extensive lymphatic circulation[4] which is important in myocardial function and pathology. The integrity of the cardiac lymphatic system has been shown to be essential to the removal of injected autologous blood and its breakdown products from the myocardium.[4] The present study further elucidates the role of the cardiac lymphatics in the reparative process after myocardial infarction and in the reaction to foreign bodies.

Significant differences were observed in the histologic evolution of myocardial infarctions between the animals with cardiac lymphatic obstruction and the controls (without lymphatic obstruction). The crude measurements indicated that the size of the infarct was generally larger



Fig. 5B. Dog with lymphatic obstruction 42 days after ligation of coronary artery branch. Note the many dilated thin-walled vessels in and about the suture granuloma. Hematoxylin and eosin. ×150

caused by intercurrent infection and localization of inflammation in an area with decreased lymph drainage also merits consideration.[1,10]

The infarct in dogs with impaired cardiac lymph flow almost always included the deeper portion of myocardium and the adjacent endocardium in that part of the ventricular wall rendered ischemic by the occlusive ligature. In contrast among animals which served as controls a thin layer of normal myocardium was consistently present between the endocardium and the infarcted myocardium.[6,7] This difference identifies the role of the lymphatics in restricting the extent of the necrotic process invoked by myocardial ischemia. This protective action could derive from prompt removal of excessive interstitial fluid which if allowed to accumulate might serve to enhance ischemia.

The state of the lymphatic drainage also plays a role in the reparative processes after myocardial infarction. Thus the fibrotic reaction in the infarcted area was increased in the dogs with impaired lymph drainage. Areas of cartilaginous metaplasia in 2 of the dogs with lymphatic obstruction indicates that in such animals participation of elements of connective tissue in healing was greater than in the control animals. This difference was also reflected in increased retention of isolated atrophic myocardial fibers heavily encrusted with calcium salts in the scars of dogs with lymphatic obstruction.

It is not apparent why impairment of cardiac lymph flow favors deposition of calcium in the scars invoked by myocardial infarction. Such impairment of flow may augment the accumulation of acid mucopolysaccharides which commonly occurs after tissue injury and this accumulation in turn may be important in facilitating calcification. Some structural form of the muscle fiber remains during early necrosis and there is a gravitation of calcium and phosphate ions to these areas as they are liberated during the process of necrosis. With impaired lymph drainage there may be a barrier to diffusion of these ions and the local increased concentration could lead to calcification.[9]

The augmentation of the myocardial epicardial reaction to silk suture material in the dogs with impaired lymph drainage was also significant. In the dogs with obstructed lymph flow the acute inflammatory response was greater and more rapid in appearance. The foreign body granuloma was larger and occurred earlier. The pleural pericardial adhesions were denser. In the dogs with lymphatic obstruction the granulation tissue meshwork was denser and included substantial portions of the adjoining epicardium; more giant cells and more fibrosis were present. In the foreign body granulomas of dogs with coronary artery ligation which were sacrificed on the forty second postoperative day focal accumulations of PMNs ("microabscesses") were present; similar lesions were not observed in animals sacrificed at earlier periods nor were they encountered among otherwise comparable dogs with unobstructed lymphatics.

In the control dogs at this time the granulomas invoked by reaction to the silk ligature were well circumscribed and completely infiltrated with chronic inflammatory cells; the silk fibers were partly removed by macrophages. As in the infarcted regions of the myocardium the macrophages and other chronic inflammatory cells apparently remained in the affected areas much longer when the lymphatics were obstructed. These alterations in the healing process combined with persistent local edema presumably produced a lesion larger than would otherwise be expected. The larger lesion in turn interfered additionally with an already compromised vascular supply.

These results fortified by those of previously reported studies carried out in this department[1,3,4] prove that lymphatic obstruction presumably alters adversely the healing processes of the heart. Myocardial infarcts produced in dogs with obstruction of lymph flow are larger and show a more marked fibroblastic reaction and connective tissue proliferation with metaplasia than do those in control animals. The infarct often includes that portion of the subendocardial myocardium commonly spared when the lymphatics are unobstructed. The foreign body response to the silk ligature used to occlude a branch of the coronary artery was also

more marked in dogs with obstructed lymph flow This latter finding suggests that impairment of lymph flow may contribute to granulomatous reactions associated with myocardial inflammatory processes in man The possible relevance of these findings to the pathogenesis of certain inflammatory and infectious diseases (e g rheumatic fever bacterial endocarditis myocarditis etc) which affect the heart in man are worth noting [1] In another study it was observed that dogs with chronic obstruction to cardiac lymph flow are much more susceptible to staphylococcal valvular endocarditis than are normal controls [9]

Results of the present study also suggest that both the size of the infarct and the nature of its healing may be influenced by the state of the cardiac lymph drainage Subendocardial infarction particularly may be more likely to occur and to be more extensive when lymph flow is impaired

Summary

Myocardial changes after an acute coronary arterial occlusion have been studied in two groups of dogs In one group obstruction to the cardiac lymphatic drainage had been produced prior to the coronary occlusion In the second group no such obstruction to lymph flow was induced The myocardial changes in the two groups were different especially with regard to the extent of necrosis the sequence of inflammatory reactions and the degree of fibrotic and calcific change

Significantly different also were the reactions in the tissues around the silk used to ligate the coronary artery branch Characteristically dogs with obstruction to cardiac lymphatic drainage had increased inflammatory response to the presence of this foreign body resolution of this inflammatory response was interrupted about 40 days postoperatively by an influx of PMNs The possible role of obstruction to cardiac lymphatic drainage in predisposing the human heart to infection and inflammation is suggested

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Electrocardiographic and pathologic changes after cardiac x-irradiation in dogs

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Myocardial tissue has been considered to be among the most radioresistant in of the body.[1] Consequently, therapeutic x-irradiation of nearby structures has been considered to be relatively free of untoward cardiac complications.[2] The limits to which this hypothesis is correct have not been well defined.

With more potent sources of radiation now in wide therapeutic usage, these parameters are worth further consideration. The following report suggests a lower threshold in the heart to acute radiation damage than that previously entertained in the literature.

This is illustrated by examples of the lesions produced and electrocardiograms of gross damage. *This is considered also* in light of one recent report that has suggested radiation as a method for the experimental production of myocardial infarction.

Methods and materials

As a *pilot survey*, 8 male dogs were subjected to acute high-dosage precordial x-irradiation under sodium pentobarbital anesthesia. Information from 7 of these animals studied for periods ranging up to 70 days after the acute exposure to radiation is included in Table I. The eighth dog received 5,000 roentgens to the anterior thorax through a field excluding the heart. At sacrifice on day 70, the heart and ECG of this animal were entirely normal.

The dogs reported in Table I were all acclimated mongrel males which weighed between 5.2 and 12.2 kilograms. They were given intravenous sodium pentobarbital for the initial irradiation and recording. Subsequent serial electrocardiograms were taken under intravenous sodium thiopental anesthesia. Standard limb leads and precordial leads were taken *using subcutaneous needle electrodes.* Lead II was taken discontinuously on a number of these dogs during the course of actual irradiation and on 2 additional dogs receiving 50,000 and 100,000 roentgens to the heart. This recording was done with a Telemedics remote transmitting receiving unit.

Irradiation was implemented with a standard x-ray tube operating at 184 kv., 30 Ma., with a filament to mid heart

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distance of 19 to 23 cm depending on the port of exposure used and the relative position of the heart in relation to the chest wall. Filtration was 0.28 mm Cu and 0.50 mm Al with a half value layer of 0.6 mm Cu. The diameter of the cone which was placed directly against the chest wall was 3.1 or 6.5 cm. The depth dose delivered to the heart was determined on the basis of the above mentioned factors

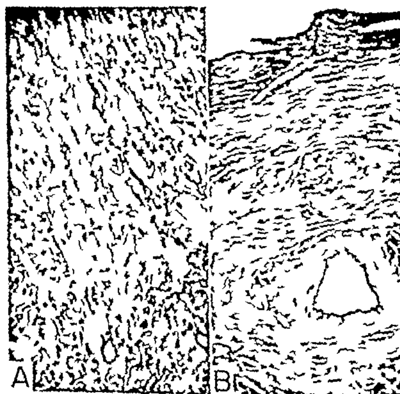




Fig. 3. [illegible] A and B. T[illegible] from the [illegible] far[illegible] [illegible] thened. C. B. Coronary arteries [illegible] the p[illegible] dual [illegible] the site of the [illegible] Hematoxylin and eosin stain.

Table I. Electrocardiographic findings

Dog	Dosage to heart (roentgens)	Port	Cone diameter (cm.)	Time interval (days)	Rate	P R	QRS	Q T
						(sec.)		
1	7,000	Anterior	6.5	0	140	0.10	0.05	0.24
				11	150	0.10	0.05	0.20
2	7,000	Anterior	6.5	0	160	0.09	0.03	0.20
				24	160	0.08	0.11	0.16
3	8,019	Anterior	3.1	0	140	0.08	0.04	0.22
				14	120	0.08	0.07	0.28
4	5,000	Lateral	3.1	0	160	0.08	0.03	0.20
				56	110	0.12	0.05	0.22
5	5,000	Lateral	3.1	0	105	0.10	0.04	0.22
				70	165	0.10	0.05	0.19
6	7,000	Lateral	3.1	0	80	0.11	0.05	0.24
				56	120	0.10	0.06	0.22
7	[illegible],000	Lateral	3.1	0	100	0.10	0.05	0.28
				70	135	0.11	0.06	0.20

and estimated position of the center of the heart.

In 3 of the dogs an anterior port was used with the dog held by clamps in a supine position. The overhead cone was placed so that its midpoint centered an oblique upward running line between the apex point of maximum cardiac impact and the midline of the mediastinum at the approximate level of the base of the heart.

The remaining dogs were irradiated through a lateral port from below while they were in a left decubitus position. Thus they were lying on their left side in direct contact with the cone. A vertically oriented tube irradiated upward. This was centered over the midventricular region of the heart as determined by palpation of the apex beat. This positioning was calculated to provide the maximum volume of ventricular heart tissue in close proximity to the chest wall and the contingent source of radiation.

Estimated tissue dose at the midseptal region of the ventricles varied in different animals from 5,000 to 8,000 roentgens. Dosage, position, and diameter of the cone are summarized in Table I.

Electrocardiograms were made prior to and immediately after irradiation and in some during irradiation. These tracings were compared with subsequent tracings made under standard conditions at varying intervals up to 70 days after the irradiation.

Axis (deg rees)	Q waves (lead)	Interpretation	Gross and microscopic changes
+ 75 + 60	aVL aVF I II V aVL I II V[illegible]	No significant change	Pericarditis anterior right ventricle full thickness lesion large areas of hyaline degeneration venous exudate RBC extravasation
+ 85 + 85	aVR aVF II III aV III	Right ventricular conduction defect interventricular septal disease	Pericarditis with hydropericardium lesion of entire lower right ventricle and right interventricular septum necrosis inflammatory reaction fibrosis
——— −170	——— aVR aVL V[illegible]	Right ventricular conduction defect anteroseptal infarction	Pericarditis (serosanguineous) entire right ventricle except base right interventricular septum and portion of apical left interventricular septum inflammatory lesion with necrosis
+ 60 + 75	V V II III aVR aVL V	No significant change	Slight mottling posterior left apex no gross lesion focal hyaline change and extravasation of red blood cells
+ 75 − 45	II III aVR aVF I aVR V V V	Left ventricular conduction defect lateral wall necrosis	Lateral apical left ventricular lesion with fibrosis scattered hyaline and vascular changes
+ 75 − 30	I II III aVF II III aV V[illegible]	Left ventricular conduction defect	Anterolateral apical left ventricular infarct focal areas of necrosis
+ 85 − 5	II III aVF aVR aVL V V	Left ventricular conduction defect lateral wall necrosis	Pericarditis anterolateral apical left ventricular infarct with thrombus on endocardial surface marked necrosis and fibrosis

After the final electrocardiograms were taken the animals were sacrificed with an overdose of sodium pentobarbital and the hearts were examined grossly and blocks taken for microscopic examination

Results

The gross and microscopic changes observed in these hearts at the time of sacrifice are summarized in Table I along with the electrocardiographic changes The abnormalities observed were as follows

Gross anatomy Six of the 7 hearts revealed gross signs of external damage The seventh (Dog 4) showed only a slight mottling of the apical epicardial surface over the posterior aspect with no gross evidence of a lesion on section of the wall The other dogs exhibited varying lesions and severity of reaction Hydropericardium was seen in 2 (one serosanguineous) and gross pericarditis in 4 with marked thickening increase in vascularity and reactive attachment at the site of the epicardial lesion The epicardium showed gross indication of damage in 6 of the dogs The involved areas and the extent of the damage varied from dog to dog

The port of exposure determined which chamber was predominantly involved The dogs which were irradiated through the anterior port showed lesions which varied from those which covered a 3 by 4-cm area over the anterior right ventricu

lar wall to those involving almost the the entire ventricle and portions of the interventricular septum The areas involved were grossly mottled dark red to gray On section frequently the entire thickness of the wall appeared to be involved and these areas in 2 of the 3 cases extended into the interventricular septum and in 1 to the left ventricular endocardium near the apex The endocardium showed focal hemorrhagic areas Two of these 3 animals were irradiated with the cone that was 6 5 cm in diameter

The 4 dogs irradiated through the lateral port where the smaller cone of 3 1 cm diameter was used showed more circumspect lesions Pericarditis was seen in only 1 of these 4 whereas it was present in all the dogs irradiated anteriorly

Gross epicardial lesions were present in 3 of the 4 Distinct areas of tissue injury were most evident on the anterior lateral wall of the left ventricle in the region extending down toward the apex Epicardial reactivity ranged from marked induration and mottling of the surface to gross areas of fibrosis as large as 1 by 1 5 cm On section the mottled appearance extended through the thickness of the wall In 1 heart there was marked subendocardial hemorrhage and an irregular unorganized thrombus (Fig 1 *C*) In the fourth the myocardium appeared to be darker on the posterior surface of the left ventricle near the apex but no gross lesion was seen

No abnormalities were noted in the appearance of the basal portion of the heart in any of the dogs

Histology

Changes observed ranged from moderate extravasation of erythrocytes and hyaline alteration of connective tissue and muscle to marked muscular destruction and fibrosis with proliferation of connective tissue elements These changes in some areas alternated with areas of normal appearing myocardium In hearts examined at shorter time intervals after injury the inflammatory reaction was much more marked Hyaline alteration of the walls of smaller blood vessels especially veins was prominent In the latter large areas of eosinophilic exudate often surrounded the veins

Larger vessels showed less indication of alteration An example of the alteration of the blood vessels is shown in Fig 2 *B* Changes in muscle ranged from hyalinization with loss of striation to vacuolar degeneration and fibrosis (Fig 1 *A*) Connective tissue proliferation was especially marked in the epicardium (Fig 1 *B*) In general the localized changes were not unlike those seen in myocardial infarction Significant sparing of some areas was quite striking This was especially noted in reference to conduction tissue on the endocardial surface of the left ventricle The distribution of spared and damaged areas within the lesion area and the severity of reaction at different foci did not present a constant picture in relation to vascular distribution as seen in random section

Of special interest are the lesions seen in the interventricular septum in one of the dogs (Dog 2 Fig 2 *A*) Gross septal involvement on the right side extended almost to the membranous septum A block taken just below this point showed marked involvement of portions of the right bundle branch subendocardially with prominent vacuolar degenerative changes and connective tissue hyalinization This is particularly significant since this animal showed development of a right ventricular conduction defect and evidence of septal damage as seen in serial electrocardiograms

Correlated electrocardiography

I Anterior irradiation Three dogs received 7 000 to 8 000 roentgens to the right ventricle Dog 1 survived only 11 days after irradiation with no significant changes occurring in his electrocardiogram Grossly he presented a dark erythematous full thickness change in the myocardium over a 2 by 2 cm area of the anterior right ventricle with inflammatory changes in the overlying pericardium also Large areas of early hyaline degeneration of muscle were seen with prominent extravasation of red blood cells and eosinophilic exudate around veins

Dogs 2 and 3 survived 24 and 14 days respectively Electrocardiographic changes consistent with interventricular septal necrosis appeared between 14 and 21 days in Dog 2 and before 14 days in dog 3 The electrocardiographic abnormalities ob

served were (a) $S_1S_2S_3$ pattern (b) RSR in Lead V_1 (c) QRS prolongation (d) Q waves in right and mid precordial leads in Dog 3 and diminished R wave in the same leads in Dog 2 and (e) permanent S-T elevations and T wave inversion in Leads V_1 to V_4 in Dog 3. No abnormalities of rhythm or of P-R or Q-T intervals were noted. Dog 2 had the most extensive lesion and exhibited a friction rub in connection with the gross pericarditis evident at examination. Both dogs had hydropericardium and pericarditis as well as lesions which involved the full thickness of the anterior wall and extended into portions of the interventricular septum. In Dog 1 the lesion extended through the septum at the apex to the left ventricular endocardium. Dog 2 had high septal damage grossly which disrupted right bundle branch conduction tissue as noted above (Fig. 2 A). The lesions observed in these 2 dogs were early and were characterized by marked muscular necrosis and inflammatory reaction. The extent of the electrocardiographic alterations in Dog 2 are shown in Fig. 3.

II. Lateral irradiation. Dogs 4 and 5 received 5,000 roentgens to the lateral wall of the left ventricle. Serial electrocardiograms in Dog 4 revealed only T wave changes by the time of sacrifice 56 days after irradiation. In the frontal plane the mean T vector had rotated from -30 degrees on the day of irradiation to $+150$ degrees on the fourteenth day and subsequently to $+90$ degrees on the day of sacrifice. Although these T wave changes are consistent with lateral wall disease their significance remains conjectural in view of the variable nature of the T waves in the canine electrocardiogram.[4] This dog showed an area of discoloration on the posterior aspect of the lateral left ventricle but no gross lesion. Sections showed only extravasation of red blood cells and focal hyaline changes in the muscle.

Dog 5 was sacrificed 70 days after irradiation at which time marked electrocardiographic abnormalities had appeared which had not been present on the fifty-sixth day. These consisted of (a) marked leftward rotation of the terminal 0.03 second QRS vector in the frontal plane producing a leftward deviation of the mean QRS vector (b) orientation of the initial 0.03 second QRS vector rightward and inferiorly and (c) slight prolongation of the QRS duration. The mean T vector remained unchanged. The P-R and Q-T intervals were unchanged in both dogs. No ectopic arrhythmias were observed. In Dog 5 the QRS alterations were consistent with the development of a localized area of cardiac necrosis. The shift of the initial QRS vector rightward and inferiorly placed the lesion in the lateral wall. The marked leftward shift of the terminal QRS vector associated with slight prolongation of ventricular depolarization time



Fig. 2. Dog ... Sol... ... right bundle branch conduction t... from the interventricular septum. B, ... artery from the right ventricular wall. Hematoxylin and eosin stain.

was consistent with altered intraventricular conduction which commonly occurs with lesions in this location.[8] Grossly this dog showed a dark erythematous area with fibrosis on the left ventricular wall near the apex and the septum with microscopic widespread thickening of capillaries and hyalinization of focal muscle fibers.

Dog 7 received 7,000 roentgens to the lateral aspect of the left ventricle and developed electrocardiographic abnormalities similar to those of Dog 5. In Dog 6 a 20 per cent increase in the QRS duration and a 30 degree shift leftward of the mean QRS axis appeared 11 days after irradiation. The marked leftward and superior orientation of the terminal QRS vector appeared sometime between the twenty-eighth and fifty-sixth day after irradiation. The initial

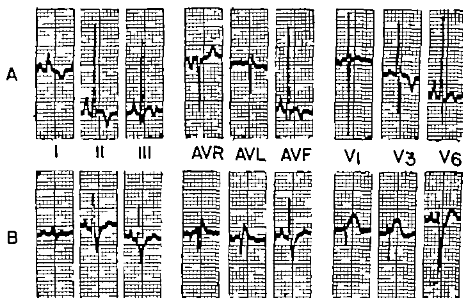


Fig. 3. Dog 2. A, Before irradiation. B, Twenty-four days after anterior irradiation.

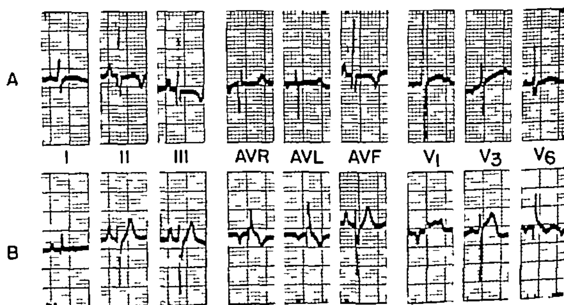


Fig. 4. Dog 1. A, Before irradiation. B, Seventy days after lateral irradiation.

QRS vector remained unchanged In Dog 7 a 25 per cent increase in the QRS duration with marked superior and leftward orientation of the terminal QRS vector appeared 14 days after irradiation The initial QRS vector became directed rightward and inferiorly These abnormalities persisted unchanged from the time of their appearance until sacrifice In both of these dogs the T wave vector shifted from its initial left and superior direction to an inferior direction by the seventh day after irradiation Although conceivably these T wave changes may have been the first indication of cardiac injury in these dogs the instability of T waves in these animals makes the hypothesis insecure There seems to be little doubt that the QRS alterations are a reflection of the localized myocardial necrosis induced in the left ventricle Fig 4 illustrates the electrocardiographic changes in Dog 7 Both of these dogs showed gross infarcts of the low anterior lateral left ventricle extending through the ventricular wall One (Dog 7) had a discrete thrombus on the endocardial surface and a wide area of adjacent ventricular wall necrosis and fibrosis The other dog had more discrete areas of gross necrosis scattered through the wall

No immediate electrocardiographic changes were seen in any of the dogs in this series This was true even in the cases of larger acute doses as high as 56 000 and 100 000 roentgens Electrocardiographic evidence of myocardial damage first appeared 14 days after a 7 000 to 8 000 roentgen dose with either a narrow cone 3 1 cm or a wide one 6 5 cm With 5 000 roentgens the electrocardiographic response in 1 case was not seen by the fifty sixth day and in the other changes were seen on the seventieth day

Discussion

The sensitivity of the heart has been controversial Many have thought that it was highly radioresistant whereas others have attributed all sorts of arrhythmias and electrocardiographic and tissue changes to cardiac irradiation [1 2 3]

The nature of the response of cardiac tissue to irradiation is nonspecific the final effect is indistinguishable from that produced by conventional infarctions [11] The damage appears to be related to the high absorption of irradiation by extracellular connective tissue particularly collagen [8 13] This is particularly significant in relation to the walls of the blood vessels so that it appears likely that vascular changes are secondary to the alteration and depletion of collagen This loss is most pronounced in blood vessels 2 weeks after irradiation [2] Although vascular pathology is central to myocardial response other factors may be involved Caster and associates observed a marked decrease in DNA and a 20 per cent loss of actomyosin in rat hearts 10 days after 700 roentgens of whole body irradiation

The stability of the cell population is another factor in sensitivity Except for vascular and connective tissue elements the heart represents a stable population Theoretically by Pack's consideration [16] an intense acute dose ought to provide an end result similar to that of spaced irradiation of the same total amount as long as the total time used is short compared to the life span of the irradiated cells In practice however large acute doses are more destructive than the same dose given fractionally This effect may be due largely to the connective tissue and vascular response in the case of the heart in which this population is subject to replacement turnover

The extent of cardiac tolerance to irradiation is widely represented in the literature Stone and associates[17] reported severe ventricular damage with clinical heart failure after 20 000 roentgens through a 4-by-4-cm port utilizing a cobalt 60 unit Moss and associates[4] found that 20 000 roentgens given through a 2 54 cm cone produced local ventricular necrosis at to 10 days in dogs However doses t 5 000 and 10 000 roentgens produced no lesions as late as days 106 and 69 respectively in their report Leach and Sugiura reported that the level of dosage effectively productive of lesions in rats was 10 000 roentgens However Michaelson reported that 1 50 roentgens produced fibrosis in the right atrium and foci of muscle degeneration in dogs irradiated in the midline Warthin in an early report thought that 500 to 700 roentgens pr

duced myocardial damage in the rat The early literature is well reviewed by Warren [] and more recent events by Jones and Wedgwood

More recently Senderoff and associates [] have reported the effects on the canine heart of doses from 1 300 to 2 700 roentgens given in divided doses It was their belief that these dosages dilated capillaries and precapillary arterioles with an increase in the number of collaterals present when hearts were examined 2 and 6 months later after an acute ligation of the anterior descending coronary artery They saw a sparing of the subepicardial region in contrast to the full thickness infarcts in the control dogs Dogs receiving the same dosage 1 300 to 2 700 roentgens in divided doses through two ports over 14 to 17 days showed no indication of muscle necrosis fibrosis or vascular obliteration at 1 year No alterations in the electrocardiogram were noted in this period

Davis [] giving about 35 000 roentgens over 8 weeks through an 8 by 8 cm anterior port in a dog saw marked myocardial necrosis and vascular change in the right atrium Jones and Wedgwood[] have pointed out the paradox of clinical reports of involvement of the heart with doses which are relatively low in comparison to those that will produce lesions experimentally in animals Our own findings although of a preliminary nature do suggest that the acute cardiac morbidity dose is lower than it was previously considered to be and is on the order of 5 000 to 7 000 roentgens for the dog Further work may well revise this figure downward It is problematical what this much acute dosage represents in terms of chronic time spaced irradiation

The electrocardiographic evidence of irradiation damage has been variable and controversial to date Moss and associates showed intermittent left bundle branch block in one dog 10 days after 20 000 roentgens Q deflections S T elevations and T wave inversions in Leads II III and aVF were observed at 15 and 21 days after irradiation in 3 dogs and were associated with localized areas of necrosis Up to now this was the sole report of conclusive electrocardiographic evidence of myocardial necrosis after cardiac irradiation

In this report we have shown that all of the dogs which received 7 000 to 8 000 roentgens to the heart and survived for a minimum of 14 days developed electrocardiographic changes of localized myocardial necrosis The 2 dogs which received radiation through an anterior port developed electrocardiographic evidence of septal infarction The other 2 which received radiation through a lateral port demonstrated electrocardiographic changes of a lateral wall infarction as did also one of the 2 dogs which received only 5 000 roentgens

There have been a number of reports on electrocardiographic changes associated with thoracic irradiation in human beings In no recorded instance have there been electrocardiographic abnormalities indicative of myocardial infarction after irradiation that could be attributed to the radiation Vaeth and associates[] reported on 20 patients who received 1 000 to 6 500 roentgens to the heart Of the 4 who developed nonspecific T wave abnormalities one came to autopsy 7 months after 6 100 roentgens were given to the heart and showed no abnormality that could be attributed to the irradiation

Blumenfeld and Thomas [] reported a case in which 4 400 roentgens were administered to the heart (3 800 at one time) with the end result of marked pericardial effusion epicardial reaction and focal myocardial fibrosis Nonspecific S T and T wave changes were the only electrocardiographic abnormality Catterall and Evans described 9 patients receiving 3 000 roentgens to the heart over 3 weeks who developed T wave abnormalities within 4 months these completely disappeared by 1 year No postmortem examination was performed in any of these cases Others such as Jones and Wedgwood and Whitfield [] have noted transient T wave abnormalities after cardiac irradiation coincident to thoracic irradiation for carcinoma of the breast

The disparities in bridging information from experimental animal irradiation to clinical cardiac irradiation experience are obvious but this does not detract from the suggestion of Moss and associates that acute irradiation be used for the study of the myocardial infarction proc

Stone and associates[17] have already utilized cardiac irradiation as a technique for producing isolated or combined right and left ventricular failure in dogs. It represents an excellent nonoperative way of inducing a lesion that is anatomically reasonable in extent and location. Work in this direction may far better delineate the nature of cardiac radiation damage and the minimal effective dosage for and time sequence of its production.

Summary

Electrocardiographic and pathologic information is presented on 7 dogs which received precordial x irradiation of 5,000 to 8,000 roentgens delivered acutely to the heart. The nature of the induced lesions and the concomitant electrocardiographic alterations produced are the subject of this report.

Pathologic and electrocardiographic evidence of myocardial necrosis was seen in 5 out of 7 of these dogs. From this information it is suggested that the sensitivity of the heart to x irradiation is greater than has been reported previously in the literature.

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Case reports

Abnormal Q waves simulating myocardial infarction in diffuse myocardial diseases

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It is generally appreciated that diffuse myocardial disease can alter the normal electrocardiographic pattern, producing particularly P-R and ST-T changes. On the other hand, the presence of deep abnormal Q waves is believed ordinarily to be fairly specific of more extensive localized necrosis such as that seen with infarction. Recently, however, we have observed 2 patients with diffuse myocardial disease who have exhibited such Q waves in the absence of coronary artery disease or of gross areas of infarction. Our purpose herein is to call the clinician's attention to this occurrence.

Case reports

Case 1. A 29-year-old Caucasian male truck driver was admitted to the hospital on April 12, 1962, complaining of shortness of breath. He had felt perfectly well until 2 months before hospitalization, at which time he had developed an upper respiratory infection characterized by fever, malaise, myalgia, sore throat, cough, vomiting, diarrhea, and dull continuous pain in the left side of the chest. These symptoms gradually diminished during the following 2 weeks, but slight malaise continued. His condition again worsened 2 weeks before entry into the hospital and was this time marked by dyspnea on exertion and cough, slight fever, and chest discomfort. The dyspnea gradually worsened, and by the time of admission he had become severely orthopneic and suffered from paroxysmal nocturnal dyspnea.

Initial hospital examination revealed an acutely dyspneic man with a blood pressure of 90/60 mm. Hg and an irregular heart rate of 120 beats per minute. Signs of pleural effusion were present. Reduced precordial activity, distant heart sounds, and a gallop rhythm were noted. Edema, hepatomegaly, and venous distention were notably absent, and the remainder of the examination was normal.

Pertinent laboratory findings are summarized as follows. There was a slight elevation of the white blood cell count to 12,450 per milliliter with a normal differential count. Blood urea nitrogen rose from 25 to 95 mg. per cent during the patient's hospital stay. Serum glutamic oxaloacetic transaminase ranged from 95 to 170 units. A chest roentgenogram showed cardiomegaly with pulmonary edema and bilateral pleural effusion. Electrocardiograms recorded on admission and on April 16 (Fig. 1) showed sinus tachycardia with multiple supraventricular premature contractions, widened QS deflections in Lead [illegible] through [illegible], and T-wave inversion in Lead [illegible] and [illegible], with [illegible] waves in Lead II, III, and aVF. These changes remained stable until April 18 (Fig. 1), when Q waves appeared in Leads I, II, and V_6, together with an upright R in Lead aVR. Concomitantly, a QRS conduction delay to 0.12 second also appeared. The precordial leads reflected the increased QRS duration but were otherwise unchanged.

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Despite supportive therapy which included digitalis, vasopressors, and adrenocorticoids, the patient's course in the hospital was one of progressive deterioration. He became more hypotensive, showed an intermittent fever curve with a peak of 103.6° F., and developed Cheyne-Stokes respiration and cyanosis. Finally, on April 18, 6 days after admission, his pulse became extremely weak and dyspnea and cyanosis became severe. He died within a short time as a result of abrupt cessation of heart contraction.

On necropsy, the heart weighed 4 0 grams with dilatation of all the chambers. The myocardium was soft, red, and studded with petechiae, with slight hypertrophy of the papillary muscles. When incised, a large amount of serosanguineous fluid exuded from its cut surface. The left ventricular free wall was approximately 11 mm. thick and presented no areas of gross localized necrosis. The coronary arteries were normal. Microscopic examination of the myocardium revealed separation of the myocardial fibers, diminution of cross striations, and occasional smudged eosinophilic casts in the fibers. One focus of smudgy eosinophilic connective tissue in the myocardium was noted. The remainder of the necropsy showed the usual concomitants of congestive heart failure, and, in addition, several infarcts of both kidneys were noted. The final impression was idiopathic myocardiopathy; a viral origin could not be excluded.

Case 2. A 21-year-old Caucasian male had been followed intermittently in this institution since the age of 3 years, at which time the diagnosis of pseudohypertrophic muscular dystrophy was established. He developed progressive symptoms of congestive heart failure during the last 9 months of his life, characterized by exertional and nocturnal dyspnea, orthopnea, ascites, and pleural effusion. He had never experienced chest pain, nor did he give a family history of heart disease, hypertension, or strokes. Two hospitalizations were required during this period for control of the heart failure. When examined in December, 1967, during his final hospitalization, he had a blood pressure of 80/60 mm. Hg and an irregular heart rate of 80 beats per minute. Bilateral pleural effusions, severe hepatomegaly, and distention of the neck veins were present. The precordial impulse was diffuse and the heart was minimally enlarged to percussion. Heart sounds were distant, and a protodiastolic gallop was audible. Typical changes of far advanced muscular dystrophy with generalized muscle atrophy were obvious, although he was able to ambulate to a limited extent in a wheel chair.

Moderate generalized cardiomegaly, pulmonary vascular congestion, and bilateral pleural effusions were visualized on the chest roentgenogram.

Electrocardiograms were recorded intermittently from June, 196 , until shortly before the patient's death, and all of these revealed approximately the same pattern: a QR in Lead I and extensive QS deflections in Leads II, III, aVF, and V through V (Fig. 3). The rhythm varied from atrial flutter to atrial fibrillation with varying atrioventricular block and episodes of nodal rhythm (Fig. 2).

During his final hospitalization, attempts to improve his cardiac compensation met with little success. Two weeks after his discharge from the

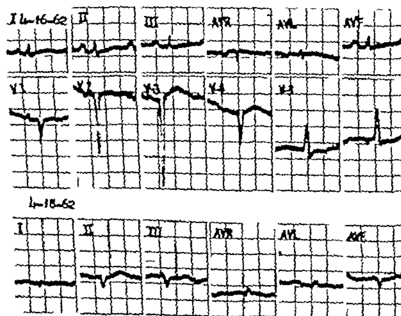


Fig. 1. Case 1. The ECG shows extensive QS deflections across the entire precordial leads. Two days later (4/19/6) these abnormalities are joined by additional QRS changes in the standard and limb leads, together with a delay in conduction, suggesting extension of n al   t

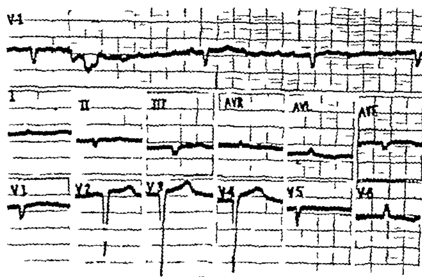


Fig. 2. Case 2. The ECG shows deep Q waves in many leads suggesting both anterior and lateral infarction.

hospital in January, 1963, he died at home and permission for postmortem examination was not obtained.

Discussion

As one can see from the electrocardiograms taken in both cases, deep Q wave patterns with loss of R waves existed in extensive distribution, rendering it impossible to discern these changes from those classically seen in infarction of myocardial tissue. In the first case, necropsy proved the absence of infarction and in the second the age of the patient plus the over-all clinical picture virtually eliminated infarction from consideration.

Pruitt and associates[1] recently have called our attention to the occurrence of electrocardiographic changes in idiopathic myocardiopathy which closely simulate those in apicolateral myocardial infarction. Their 3 cases showed electrocardiograms with deep Q waves in the lateral chest leads with a tendency for high R waves in Leads V_1 and V_2. In their 2 cases studied anatomically, severe thinning and fibrosis were found predominantly in the apicolateral regions of the left ventricle. These workers, citing supporting experimental data, postulated that the relatively localized area of myocardial destruction might give rise to a loss of positive electrical forces even if it included only portions of the ventricular wall superficial to the columnae carneae. In our first case, which probably falls into the same general disease classification of "idiopathic myocardiopathy," the Q wave pattern of infarction could have been simulated through the same mechanism, although the amount of myocardial destruction in the areas underlying the Q waves did not appear to be nearly so great as in Pruitt's cases. More likely, another mechanism producing Q waves was operative in our case, viz., conduction disturbances brought about by diminutive destructive lesions resulting in aberration of the initial portion of the QRS vector. Goldman,[2] reporting 2 cases of myocarditis simulating myocardial infarction, observed that one patient also showed anterior wall QS deflections and the necropsy findings were similar to those seen in our first case.

Sanders[3] has noted that in 2 of 27 cases of idiopathic disease of the myocardium, deep QS deflections were manifest in Leads V_1 to V_4, and Dye and associates[4] also mention the presence of abnormal Q waves in 3 of 32 cases of primary myocardial disease. Nevertheless, pathologic Q waves in diffuse primary myocardial disease must be quite uncommon, for in other large series such changes were not mentioned.[5-7]

Pseudohypertrophic muscular dystrophy

is often associated with cardiac changes which closely resemble the skeletal muscle abnormality and various electrocardiographic aberrations are common[8,9] Abnormally deep Q waves in the limb and lateral chest leads are often seen but these usually occur in association with normal or high R waves across the precordium which are frequently strikingly high in Leads V_1 and V_2 This is in contrast to the findings seen in our second patient who exhibited extensive loss of R waves

Other diseases leading to diffuse myocardial replacement or damage have been reported occasionally in association with abnormal Q waves These diseases include scleroderma[10,11] Friedreich's ataxia[12] and amyloidosis[13,14] Thus it behooves the clinician to bear in mind that the presence of abnormal Q waves is not necessarily synonymous with ischemic heart disease with localized infarction

Summary

Two cases are presented in which deep QS deflections in multiple electrocardiographic leads simulated myocardial infarction Both patients had diffuse myocardial disease in one the cause was unknown and in the other the condition was associated with pseudohypertrophic muscular dystrophy It is pointed out that diffuse myocardial destruction or replacement from several causes can occasionally give rise to deep impressive Q wave changes

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Lodged catheter during cardiac catheterization

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Many and varied are the reports of complications of cardiac catheterization. Among them are subendocardial hemorrhage, local thrombosis[1] including septal wall thrombosis after transseptal puncture[2], transient and more persistent arrhythmias, heart block, ventricular fibrillation progressing to cardiac standstill, cerebral emboli,[4,7] peripheral vascular emboli, accidental air embolism to the brain, intracardiac knotting of the catheter,[9] fever and bacteremia,[10] hemoptysis, vasovagal reaction, pleural pain and effusion, pneumonitis, pneumothorax, hemopericardium,[11] and cardiac tamponade,[12] have all been associated with percutaneous needle puncture of the left side of the heart. The catheter has caused serious impairment of blood flow through a severely stenosed pulmonary valve,[4] has interfered with coronary artery blood flow,[15] has been associated with pulmonary artery thrombosis,[17] has led to death in patients with primary pulmonary hypertension,[19] and has produced spells of cyanosis and unconsciousness in patients with Fallot's tetralogy.[8] Ventricular and atrial perforations have occurred.[5] Post-pericardiotomy syndrome has been reported.[20] As well, there have been reports of small polyethylene catheters causing emboli from peripheral vessels to lodge in the heart[21] and of intracardiac amputation of catheters used in left atrial puncture.[3]

We report here the temporary lodging of a No. 7 Cournand catheter with the tip at the junction of the superior vena cava and the right atrium, and with the area of apparent fixation at the level of the clavicle. This has not previously occurred in more than 3,000 catheterizations done in our Adult Cardiology Department.

Case report

A 29-year-old Negro woman with a history suggestive of rheumatic fever at age 6, and recent fatigue, was admitted on Aug. 8, 1963, for cardiac catheterization. Of pertinence in her physical examination was a Grade 2/6 holosystolic murmur over the third left intercostal space, which radiated to the apex. P₂ was greater than A₂, with a split second sound. The blood pressure was 120/70 mm. Hg, and the heart rate was 19/4 and regular. Electrocardiogram and chest fluoroscopy with barium swallow were normal. The clinical diagnosis was interventricular septal defect.

At cutdown, the right basilic vein was entered by cutdown with a No. 7 Cournand catheter, and this was advanced with ease to the right atrium and inferior vena cava. As the catheter was being rotated and simultaneously advanced into position in the inferior vena cava just caudad to the right half of the diaphragm, it came to an abrupt standstill. With further manipulation it withdrew so that the tip lay free at the junction of the superior vena cava and the right atrium. Here it lodged securely, resisting further attempt at move-

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Fig. 1. Arrow demonstrates the point about which paradoxical movement of the catheter could be demonstrated.

ment in any direction. A drip of 0.1 mg. per cubic centimeter of heparin solution was begun through the catheter. A hot water bottle was applied to the upper arm and axilla and an additional 50 mg. of meperidine was administered. (Premedication included 100 mg. of secobarbital orally and 50 mg. of meperidine intramuscularly.) It was decided to proceed with the retrograde study of the left side and then return for removal of the catheter. A No. 7 National Institutes of Health catheter was passed into the left ventricle via the right brachial artery, and while the patient was being positioned for selective angiography the tip spontaneously advanced through a [illegible] defect in the septal wall into the right ventricle. Having completed the study of the left side we turned again to the stuck catheter and were presented with the same resistance. The patient complained of severe pain in the axilla and upper arm medially when more forceful manipulation was attempted. She was returned to her room and several hours later another unsuccessful attempt was made after the administration of 50 mg. of meperidine. Prophylactic penicillin was given, and the lumen of the catheter was kept patent with a slow drip of heparin solution. Twenty-four hours later a further attempt after the administration of tolazoline hydrochloride 25 mg. intravenously ended in failure. The patient was scheduled for surgical removal of the catheter the next day with preparation for possible thoracotomy.

Forty-five hours after the insertion of the catheter the patient was given a right stellate ganglion block with 6 c.c. of 1 per cent Xylocaine [illegible] [illegible] and epinephrine 1:100,000. Twenty [illegible] the catheter with the [illegible] through all positions of the shoulder and with the [illegible] arm rotated, flexed, and extended was [illegible]. Pentothal 150 mg. was administered, followed by nitrous oxide and oxygen and then Fluothane in a semiclosed system. Under general anesthesia with the patient's arm abducted to 90 degrees the catheter was withdrawn 9 to 10 cm., gave a sudden jerk, and then withdrew with ease. The patient was discharged 3 days later with no complaints referable to the procedure and with the chest x-ray film unchanged.

Discussion

We can only conjecture as to what happened when the catheter became immovable. It should be stressed that the catheter was manipulated very little before it became lodged. Spasm in the brachial artery so that the vessel closes down on the catheter is not uncommon, and this occurs in the smaller radicles of the brachial venous system as well. We have never seen spasm with resultant lodging of a catheter in the larger venous trunks within the thorax. Our case was treated initially as brachial venospasm with temporary interruption of manipulation to prevent further aggravation and with the application of external heat. Gentle manipulation after these techniques was ineffective. More forceful attempts revealed that the point of fixation was really in the subclavian vein—a vessel far too large to constrict down on the catheter. The catheter was checked for flaws in its surface before use and again with the fluoroscope coned down to a small field which was moved along its length. Contrast material was injected and flowed freely from the tip without evidence of extravasation along the catheter. On attempted movement of the catheter a point at which the clavicle, first rib, and catheter were superimposed (Fig. 1) seemed to act as a fulcrum with paradoxical movement of the tube beyond this point. An anatomic constriction of the vessel could be postulated to have existed here. No pain was elicited in this area by manipulation. However, the excruciating pain produced in the axilla and upper arm was probably the result of the taut catheter impinging upon a nerve bundle or pain-sensitive structure in that region.

The catheter was examined after removal and a 5-cm. sleeve of tissue was noted beginning about 10 cm. from the

tip This material was removed piecemeal and sent for pathologic sectioning The catheter beneath was free of irregularity The pathologic diagnosis was tissue fragment consistent with intima of vein It would appear that during rotation of the catheter the intima of the subclavian vein or a valve leaflet (a pair of valves is usually situated about 2 5 cm from the termination of the subclavian vein) was picked up and wrapped about the catheter where it locked securely in place Surface tension possibly also played a role the catheter and intima being held together by a thin film of blood between them just as two pieces of glass may become bound tightly together by a thin film of fluid The catheter was removed only by tearing this length of intima from its bed without apparent further complication

Summary

A No 7 Cournand catheter became lodged in the subclavian vein requiring removal under general anesthesia It was found to have been held by a cuff of vessel intima which was torn out when the catheter was dislodged

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Salmonella infantis infection of a pre-existent ventricular aneurysm

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Salmonella infections have been of growing interest to bacteriologists, pathologists, and clinicians because of their complex and biologically revealing immunologic and genetic characteristics, their variegated and often bizarre clinical and pathologic manifestations, and their cryptic host relationships. This group of infections has been the subject of a number of fine reviews.

Ventricular aneurysms have similarly been of increasing interest both to the cardiologist and the cardiac surgeon because of recent reports of successful surgical correction of some of these lesions.

The present case is one in which a ventricular aneurysm was the site of bacterial endocarditis. It is reported not so much because of the rarity of endocarditis at this site but because the infective agent was a Salmonella. Considered in the light of certain other forms of salmonellosis and the fact that of the other two reported cases of aneurysmal endocarditis one was caused by a Salmonella, the present case is thought to represent more than a mere curiosity, and from its pathology inferences of possible pathogenetic significance will be drawn.

Case report

A 38-year-old white college professor was admitted to St. Vincent's Hospital because of his [illegible] fever and hypotension.

His illness began 3 weeks before admission with an episode of fever, vomiting, and diarrhea which subsided spontaneously in a week. During the next 2 weeks, however, he remained at home because of apathy, weakness, persistent hypotension, and intermittent bouts of low-grade fever and chills unresponsive to a short course of a broad-spectrum antibiotic and an injection of penicillin. His gastrointestinal symptoms did not recur, nor did he complain of any other specific symptom. On the day of admission, having manifested no mental or emotional changes hitherto, he awoke confused and obtunded. Shortly afterward he had a severe rigor and a temperature of 10[illegible] F.

No one with whom the patient had been recently associated had had gastrointestinal symptoms.

The past history was negative save for a partial gastrectomy 9 years earlier for a complication of what appeared to have been a congenital malformation of his stomach. Symptoms compatible with myocardial infarction, angina pectoris, or [illegible] failure were denied; in fact, until his terminal illness the patient had been an [illegible] vigorous man, having had the habit of walking several miles to work nearly every morning. Specific questioning as to a possible cardiac episode during the surgical admission revealed nothing suggestive.

Physical examination: The patient was an acutely ill and ill-aged man, dehydrated, flushed, and pink, who was pleasant and cooperative but quite confused. The temperature was [illegible] F, the pulse was 90

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Irregul the bl od pre ure w 90/60 mm Hg nd the re pir t were 24 nd regul r

The posit e finding were onfined to the heart and entral nervou s tem There was a vi ible and e ily palpable s tolic bea e in both the fourth and fifth left intercostal paces at about the mid la scular line which w readily di tinguishable from the pical impul e the latter was l cated at the nterior xillary line in the fifth intercostal pace The lower sternum w normally resonant nd there w no par sternal heave The com ponent of the sec nd sound were nowhere separ able nd the first sound t the pex was of normal ten ty A third heart sound was not heard There was a short s t lic murmur at Erb point and a hort high pit hed and scratch protodia tolic sound m ximal over the area of bnormal pre ordial pulsation The pulses were all equal and there were no ig of cardiac failure The nervou t m revealed the me tal changes noted above nd m ld weakness of the right side of the face and of the right hand The kin mucosae conjuncti ae and retinae were unremarkable There was neither plenomegaly nor lymphadenopathy

Laboratory studies Hemoglobin was 17.5 Gm per 100 ml The white blood cell count was 16 000 per cubic millimeter differential count of 75 per e t polymorphonucl rs 6 per cent band forms 17 per cent l mphocytes 2 per cent monocytes Platel ts were adequate Urinalysis showed one plus prot n no blood elements 30 to 40 granular a t pecific gra it of 1 009 Blood urea nitrogen was 60 mg per 100 ml The serum electrolytes m milliequ al nt per liter were Na 131 K 4 0 Cl 115 CO 26 5 Serum albumin was 1 7 Gm per 100 ml serum globulin 3 6 Gm per 100 ml Alka line pho phatase was 6 0 Bodan ky unit Serum glutami xal acetic tra minase w 92 unit Serum glutamic pyru transaminase was 56 units St l culture howed *Salmonella infantis* A pos tero anterior che t film revealed an enlarged heart with pr minent protuberance on the left border b the ap (see Fig 1) The electrocardiogram howed nu rh thm non pecific S T and T wave hange and m rkedly reduced QRS amplitude



Fig. 1 Post roant ro x r film f the chest on the d f lm n

without however evidence of myocardial inf rc tion

Course Eight hours after admi ion the patient suddenly spiked a temperature of 104.4 F Exami nation then revealed extremely tender purpl h lesions that a eraged 7 mm in diameter on the volar t p of eight fingers and a very loud peri cardial friction rub radiating widely over the entire chest but maximal over the abnormal cardiac pul sation Four samples of blood for culturing were d wn over the ensuing 3 hours and he was begun on travenous tetracycline and str ptomycin His temperature fell over the next few days and nev r again ro e above normal level

During the next 10 days there was a gradual im provement in his neurological status and azotemi and a slight gain in strength *Escherichia coli* was grown from all blood culture and on the ba is of sensiti ity studies chloramphenicol was sub ti tuted for tetracycline No other change was made in therapy which was otherwi e supporti e Except for wide day to-day variations n the quality and intensity of the friction rub there were no change in the cardiac findings and no evidence of heart failure developed The finger lesions faded and r appeared in dwindling degree and no new muco cutaneous lesions appeared Serial electrocardio grams were abnormal but not diagnostic of either myocardial infarction or pericard tis

On the morning of the twelfth hospital day the patient suddenly developed nodal tachycardia and hock without associated symptoms or signs A asopressor promptly restored the blood pressure to normal and the rhythm to sinus At thi time a large number of the finger pulp lesions reappeared nd pl ter hemorrhages nd petechiae appeared for the first time Once the cardiac irregularity had been corrected however the patient looked in general as he had the day before

The next morning the patient died udd enly There were no witne ses to hi death

Autopsy findi gs Examination wa limited to the chest and abdomen nd the pert nent findings to the heart and gastroi testinal tract The heart weighed 500 grams There was a l rge trul bular *saccular aneurysm involving the ntire apical por* tion of the left entricle and the adjacent w lls gross ly di torting the ove all contours of the heart (see Fig 2) The epicardial surface of the neurysm was adherent to the overlying peri ardium t its center by dense fibrous adhesio and more margi nally b fibrinous fleck The peric rdium wa otherwise normal and contained no fluid The wall f the aneurysm was from 2 to 4 mm thick wh te nd densely fib rous The aneurysm cont ined a large gray h brown thrombus wh h in some are w firmly adherent t t lining n l in other loosely so (see Fig 3) Needle puncture f the aneu rysm t a d pth of 5 mm t the it f den e adhesi ns to the pericardium yiel ed on a pir t n a few milliliters f cloudy rin fluid Sect f the thrombus howed a re of liquef t n the area und rlying the te of punct re (see Fig 3) The remainder of the left ventricle sh wed moderate hypertrophy and focal myocardial fibrosis There w moder t seg ment l athero sclerosis f the coron ry arteries and t f m l



Fig A terior (A) and posterior (B) view of the heart

point of the left anterior descending branch a zone of old occlusion with recanalization There was no evidence of valvular or infective disease elsewhere in the heart

The findings in the abdomen were a healed subtotal gastrectomy with gastrojejunostomy moderate lymphoid hyperplasia of the distal ileum and normal gall bladder the spleen had been removed surgically

Microscopic examination of the wall of the aneurysm showed it to be composed of fibrous tissue with aggregates of mononuclear and plasma cells in the area near the thrombus The adherent pericardial tissue showed a similar picture No abscess was present in any of the heart sections examined Sections through the thrombus showed it to be in the main composed of red cell ghosts platelets necrotic leukocytes bacteria-like aggregates and fibrin Necrosis was most marked in the center of the thrombus and near the endocardium and in some areas it was hyperfused Focal areas of early organization was noted in some regions in which the thrombus was adherent to the wall of the aneurysm (see Fig 4) The surface of the clot showed no endothelization The valves were normal and the myocardium showed many areas of focal fibrosis and microthrombi

Postmortem bacteriologic studies Culture of heart's blood from all chambers and of the fluid aspirated from the thrombus grew out *Salmonella infantis* in pure culture but failed to grow out *Escherichia coli* Culture of the stool grew out only normal flora

Interpretation The patient ... ventricular aneurysm was the result of an old myocardial infarction which in view of the patient's history might well have been suffered during his surgical ... 9 years before During bacteremia ... of a Salmonella enteritis the lining of the aneurysm was seeded by bacilli and vegetation began to grow at the site About this nidus of endocardial thrombotic material was laid down which itself became infected Inflammation then produced adherence of the thrombus to the adjacent endocardium while at the ... of the original nidus of infection the necrosis became so intense ... to produce liquefaction That the *Escherichia coli* organism cultured from the ... secondary invader ... attested to by the failure to culture this organism from the thrombus or from the heart's blood at postmortem

The findings might be explained alternatively by assuming that the thrombus preceded infection ...



Fig. 3 Left side of the heart and ventricular aneurysm opened showing thrombus within

tion. Were this the case, however, we believe that the thrombus would more likely be endothelized at its surface and more organized in its substance and would show ulceration or vegetations at its surface rather than maximal purulence deep in its substance and near the wall of the aneurysm.

Discussion

Ventricular aneurysm[9] is, with few exceptions, a consequence of myocardial infarction. It is present in from 10 to 20 per cent of autopsied cases and is the source of two principal complications: thromboembolism from the lesion and heart failure due to the burden of a noncontractile extra cardiac chamber. Endocarditis involving a ventricular aneurysm is rare and has been reported only twice hitherto. Smirnova and associates[10] describe a case of postinfarctional aneurysm which became the site of bacterial endocarditis in which the organism, although not specified, was most likely a gram positive coccus. Decker and Clancy[11] reported a case which clinically and pathologically was like our own: an asymptomatic patient who had had an infarct 3 years earlier died of bacterial endocarditis; at autopsy a septic thrombus was found in an old large ventricular aneurysm. In this case, as in ours, it was problematical whether a bland thrombus had been seeded during a bacteremia or whether the thrombus was secondary to endocarditis of the aneurysm, but the authors concluded, on much the same grounds as did we, that the latter had been the course of events. It is of the utmost interest that the infecting organism in this case was a Salmonella.

Clinical salmonellosis varies greatly in severity and form.[1,2,3] Differences in virulence among the species and the strong tendency of some to produce characteristic syndromes reflect the importance of infective factors in these infections. But *even more important are host factors*. More than 75 per cent of the patients with Salmonella infections have a major preexistent disease. In addition to those states which lower resistance to infection in general, such as cirrhosis, malignancy, steroid therapy, etc., certain others, for example, sicklemia, malaria and bartonellosis, induce for obscure reasons a quite specific susceptibility to the Salmonellae.[1] Their portal of entry is the mouth, and to produce infection these organisms must colonize in the bowel. Since they are quickly killed by a low pH, normal stomach func



Fig. 4 Microscopic view of junction of [illegible] wall and thrombus showing [illegible] (below) and organizing thrombus with large [illegible] of fibrin (above)

tion offers a major barrier to infection and conditions in which acidification of the ingestum is impaired are associated with an appreciably increased susceptibility to the Salmonellae.[4] There can be little doubt that our patient's gastrectomy rendered him susceptible to the infection which killed him.

Endocarditis due to enteric bacteria[13,14] is uncommon, the entire group having been responsible for only 4 per cent of 509 cases of infective endocarditis pooled from several series.[13,14] But if endocarditis due to the group as a whole is infrequent, that due to the Salmonellae must be termed rare: no Salmonella was identified among the 509 cases mentioned, and Geraci[4] cites only one in a series of 300 consecutive cases of bacterial endocarditis at the Mayo Clinic. Indeed, the indisputable cases of Salmonella endocarditis adequately reported in English total only 19, a number small enough to consider in some detail.

The relevant features of these 19 cases are summarized in Table I. It is notable that there were only three cures. Of these, 2 patients were treated with large doses of penicillin in conjunction with another agent, and the third with kanamycin after failure of chloramphenicol. *In no instance was cure achieved by the sole use of the antibiotic to which the Salmonella had been proved in vitro to be most sensitive.*[28,33] In perusing these reports one cannot but be struck by the frequency of diverse and unusual pathology. The diversity is, however, spurious, for on analysis the unusual lesions prove to be merely variants of the same entity: *mural endocarditis*. This uncommon form of endocarditis in

Table I

Case number	*Reference*	*Species of Salmonella*	*Underlying heart disease*	*Site of involvement*	*Outcome*
1	21	Schottmülleri	None	Mitral valve	Died
2	22	Choleraesuis	None	Aortic valve	Died
3	23	Choleraesuis	None	Mitral valve	Died
4	24	Typhimurium	None	Mitral valve	Died
5	25	Choleraesuis	Rheumatic mitral and aortic	Mitral valve	Died
6	26	Oranienburg	Rheumatic mitral	Mitral valve and left *atrium*	Died
7	7	Schottmülleri	Rheumatic mitral and aortic	Mitral and aortic valves Outflow tract of left ventricle	Died
8	28	Choleraesuis	Rheumatic mitral	Mitral valve	Lived
9	29	Choleraesuis	Rheumatic mitral, aortic, and tricuspid	Mitral valve	Died
10	20	[illegible]	Rheumatic mitral	Mitral valve	Lived†
11	30	Typhimurium	Rheumatic	Left atrium pre-existent thrombus	Died
12	31	Minnesota	Calcific aortic stenosis	Aortic valve and left atrium	Died
13	32?	Fayed	Congenitally deformed aortic valve	Aortic valve	Died
14	11	Choleraesuis	Bicuspid aortic valve	Aortic valve	Died
15	11	Sal. species	ASHD, ventricular aneurysm	Aneurysm of left ventricle	Died
16	Present Authors	Infantis	ASHD, ventricular aneurysm	Aneurysm of left ventricle	Died
17	11	Choleraesuis	Calcified mitral ring	Mitral valve	Died
18	29	Choleraesuis	Syphilitic aortitis with aortic insufficiency	Endocardium of left ventricle, right atrium§	Died
19	33	Sendai?	Aortic valve disease (etiology?)	Aortic valve	Lived‡

* [illegible]
† [illegible]
‡ [illegible]
§ [illegible]

the infrequent instance in which it is encountered, typically coexists with valvular endocarditis, to which it is secondary. Isolated mural vegetations are rare. The occurrence of mural endocarditis in 7 of these 19 cases is remarkable; that in 4 the mural lesions were, moreover, of the isolated type is truly striking.

It is currently believed[34] that certain local conditions of high velocity flow are requisite to the establishment of endocarditic vegetations, and that the occurrence of such hemodynamics at certain valve deformities and shunts accounts for the almost exclusive predilection of endocarditis for these locations. Similarly, the infrequency of mural endocarditis (despite the frequency of mural scarring by myocardial infarction) arises from the lack of the necessary hemodynamics at mural sites. That mural vegetations, when they do occur, typically are associated with valvular infection is no doubt due to the impingement upon the involved walls of densely septic jets originating at the already infected valves.

In only 2 (Cases 6 and 7) of the 7 cases of Salmonella mural endocarditis are the *findings typical, with the mural vegetation* occurring at loci where jets from the infected valves would impinge. In 2 other cases (Cases 11 and 18) the mural lesions were located similarly vis-a-vis jets, but the deformed valves were themselves uninfected. In yet another (Case 12), although valvular endocarditis was present, the aortic valve was the infected one, whereas the mural involvement was of left atrium. The 2 cases involving ventricular aneurysms were clearly ones of isolated mural endocarditis.

Thus, over a third of these cases of Salmonella infection present forms atypical of bacterial endocarditis as it is usually encountered; this departure from the usual pattern is due to the statistical ease with which Salmonellae establish themselves at (mural) sites statistically inhospitable to colonization of bacteria in general. It seems that these organisms have an avidity not shared by other bacteria for such mural surfaces, and that this avidity supersedes hemodynamic factors in the pathogenesis of some, if not most, of these cases of mural endocarditis. These cases, then, although they are bacterial endocarditis geographically, are *something quite different* in the pathogenetic sense. The mural sites involved—the linings of ventricular aneurysms, the ventricular wall overlying a syphilitic process, the wall of rheumatically sclerotic atrium, an atrial mural thrombus—all share the common feature of comprising endothelizations of abnormal surfaces. Viewed in this light, these cases resemble another group of cases of endovascular infections due also disproportionately often to Salmonellae: endarteritis of arterial aneurysms.

This form of salmonellosis[1, 35, 40] most characteristically presents the complex of an infected atherosclerotic abdominal aneurysm, osteomyelitis of the contiguous vertebrae, and terminal rupture through the inflammatory locus, usually into the retroperitoneal space. It is disputed in these cases whether the osteomyelitis is secondary to the aneurysmal infection or whether the latter is due to a primary osteomyelitis arising in a site of lowered resistance in a vertebra eroded by the aneurysm.[1, 35, 40] The latter interpretation fails, however, to explain the occurrence of otherwise typical Salmonella endarteritis involving aortic aneurysms in the absence of osteomyelitis,[1, 35, 34, 35] aneurysms of other arteries such as the femoral or iliac,[36] or a thoracic syphilitic aneurysm.[36] Apropos a point unexplained in our case, the blood cultures positive for *Escherichia coli*, it is noteworthy that in a series of 10 cases of Salmonella endarteritis[34] double infection was found twice, the co-infecting organism being *Escherichia coli* in one, and Aerobacter in the other instance.

If mural Salmonella endocarditis shares, on the basis of an avidity of the Salmonella organisms for certain endothelial surfaces, a common pathogenesis with these endarterial infections, then the former constitute instances of endocarditis only in the narrowest geographical sense, having little relation pathogenetically to bacterial endocarditis as the term is usually used.

Summary

A case is reported of *Salmonella infantis* endocarditis of the lining of a chronic postinfarctional ventricular aneurysm with secondary formation of thrombus about

the infected site and superinfection of the thrombus with *Escherichia coli*. The reported cases of Salmonella endocarditis are discussed and the frequency of mural and particularly of isolated mural endocarditis among them is emphasized. The high frequency of these uncommon lesions in Salmonella endocarditis is interpreted as reflecting an avidity of this group of organisms for abnormal endothelium and on this basis the suggestion is made that these endocarditic lesions may be pathogenetically more closely related to Salmonella endarteritis involving arterial aneurysms than to bacterial endocarditis in the classic sense of this term, a lesion arising under pathogenetically quite different circumstances.

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Clinical pathologic conference

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Clinical abstract

DR HEATH This patient illness began in 1954 when he was 16 ear old He felt lump beneath the right side of his jaw and went to see h general practitioner on this acc unt H was referred to surgeon who foun l spherical mobile ma s 3 cm in diameter beneath the angle of the jaw Other nodules were palpable in the axillae and in th an terior nd posterior triangles of the neck The lump beneath the jaw wa excised and a cour e of deep x ray therapy (2 000 roentgen) was given to the right and left cervical regions over the period May 11 to May 24 1954 During later hospitalization in 1962 he olunteered the information that during this course of treatment in 1954 he could not f l to not that the urses had great difficulty in pal pating the pul in his l ft wri t After thi he t tended a follow up b ix and O t 25 1955 t was noted that tw lumps both 2 cm in diameter were pre ent one in the left axilla and the oth r in the right side of the neck Nevertheless he felt generally well In 1958 he suffered an illne s of 1 week duration which was diagno ed as broncho pneumon

At the end of 1959 he began to feel unw ell and had stiffness in the neck Nodules were still present in hi neck and ax la and others were palpable n the left groin

He beg working as truck driver One day in September 1961 while be was seated in hi vehi le h sion blurred nd it seemed to him as though he were eeing obj cts through a cloud This ensation la ted for 20 minute nd he wa abl to on erve while it was going on Two month later imila ep od occurred and thi was follow ed by others t bout eekly inter l the right eye w affect d more tha the l ft On Jan 15 1962 he had sev re tta k while he w s driving This time h sion was affected to uch an extent that he uld ee o ly for a few yards in front of h m He h l aching behind both eyes and a peculiar sense tion of ucles ne s ffecting both hand and fore arm Th tt k la ted 30 minutes

In the ev ning of the same day during a meal h unnes of v ion me on again but th time the right sid of his face felt as though he had had an injection of caine and when he bit the right side of his l r lip t felt numb He was unable to continue his meal nc he could not hold the knife in h right hand He needed t rst nce to walk home one quart of mile on a count of weakne and feeling of unsteadiness in hi legs The following morning thi we kne had gone but the blurring of n rem ined H could not make out the mall prin t in the morning new paper Un ble to go to work he had repeated ttack of weakne and numbne which aff cted the right side of the body He often felt giddy when uddenly changing his po ture and on three oc ions he lo t onsciou ness momentarily He referred t a Medical Out Patient Clinic nd w s admitted to hospital for in e tigation on March 25 1962 On examination he had obviously lost weight (H id that he had lo t 12 pound) He looked ill

Many of the pul es were impalpable or weak (see Table I)

The murmur in the uprasternal l not h w a ompanied by a thrill Th he rt w s not enlarged and the heart s nd were normal

There were palpable enlarged lymph node in the left xill right gro nd submandibular regi n The enlarged nodes f lt rubbery The pleen w palpable

There were no abnormal signs r ferable to the cent al nervou s tem Tone p wer and sensation ere no m l in all areas Reflexes were all normal

The pupil reacted bri kly to light The eyes ppeared to be normal externally The fundi ap pea ed to be normal part from light edema in the central area

A biopsy of a lymph node in the left axilla was carried out on March 30 1962 H was di charged

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from the hospital April 1962 On June 22 1962 he came back to hospital for special investigation During this period he received therapy for his disease

His symptoms continued unabated with repeated disturbance of vision and feelings of weakness In July 1962 he had sharp pains in the left side of his chest which were worse on breathing and coughing His cough was productive of a yellowish sputum He had breathlessness on mild exertion He was readmitted to hospital on Aug 9 1962 On examination he was obviously very ill with rapid shallow respiration There was dullness to percussion at the bases of both lungs and bronchial breathing at the base of the left lung He had gross wasting of the limbs and buttocks and his face was hollow and sunken Rubbery lymph nodes were felt in both axillae The murmurs were still as described at the time of his previous admission

He died on Aug 18 1962

INVESTIGATIONS The urine showed a trace of protein scanty growth of *Staphylococcus albus* 5 pus cells per high power field occasional red blood cells hyaline and granular casts The *erythrocyte sedimentation rate* (Westergren) was 37 mm in the first hour The *liver function tests* showed serum bilirubin 0.6 mg per 100 ml serum alkaline phosphatase 12 units per 100 ml thymol turbidity 1 thymol flocculation 0 Culture of the *sputum* grew *Staphylococcus albus* (coagulase negative) *Neisseria* and *Streptococcus viridans* The *blood analysis* showed blood urea 39 mg per 100 ml serum Na 144 mEq per liter serum K 4.3 mEq per liter serum Cl 104 mEq per liter The *blood picture in 1954* was 5.2 million RBC per cubic millimeter hemoglobin of 98 per cent 3,000 WBC per cubic millimeter differential of 52 per cent neutrophils 2.5 per cent eosinophils 33 per cent lymphocytes and 12.5 per cent monocytes The *blood picture in 1962* was a hemoglobin of 86 per cent 10,400 WBC per cubic millimeter differential of 55.5 per cent neutrophils 5.5 per cent eosinophils 19.5 per cent lymphocytes and 18.5 per cent monocytes *Paul Bunnell test* Control 1.4—Patient 1.8 *Serum proteins* showed a total protein of 7.5 Gm per cent serum albumin of 4.3 Gm per cent and serum globulin of 3.2 Gm per cent An electrophoretic strip was normal

Discussion

DR WHITAKER When one looks at the clinical history two themes appear One is that of a chronic disease which began in 1954 when the boy was 16 years old and which manifested itself intermittently over the next 9 years finally possibly causing his death in 1962 The other theme seems to be that of neurological disease which appeared in September 1961 These two facets of the case present me with four problems What is the diagnosis of the chronic disease? How can I explain the neurological manifestations? What is the relation of the chronic disease and the

Table I

Pulses		
Site	*Right*	*Left*
Superficial temporal	Absent	Absent
Carotid	Weak	Weak
Radial	Present	Present
Dorsalis pedis	Present	Present
Systemic blood pressures (mm Hg)		
Side	*Right*	*Left*
Arm	115/90	Unobtainable
Leg	120/70	120/70
Murmurs		
Site	*Type*	
Right common carotid artery	Machinery murmur continuous throughout systole and diastole with accentuation in mid systole and mid diastole	
Left common carotid artery	Similar to that in right common carotid artery but higher pitched and fainter Diastolic component almost inaudible	
Suprasternal notch	Systolic	
Right subclavian (behind clavicle)	Systolic	
Aorta (in epigastrium)	Systolic	

neurological symptoms? Finally, what is the nature of the terminal illness?

We are told that the palpable nodules were hard and rubbery lymph nodes. The spleen was also palpable. These are the features of a lymphadenopathy. In spite of the good initial response to surgery and radiotherapy there was a later generalization of the disease process associated with enlargement of the spleen. This suggests to me that the chronic disease is one of the malignant lymphomas, probably Hodgkin's disease, but we shall also have to bear in mind lymphosarcoma, reticulum cell sarcoma, giant follicular lymphoma, and so on. The temperature chart does not show the Pel-Ebstein type of intermittent pyrexia characteristic of Hodgkin's disease, and the blood counts are not very helpful in the differential diagnosis. I think that we shall have to ask the pathologist what the results of the lymph node biopsies were in 1954 and 1962 in order to decide which of the malignant reticuloses was present.

DR. BREWER: The lymph node removed in 1954 showed the features of Hodgkin's paragranuloma (Fig. 1). Sections showed small isolated groups of reticulum cells against a background of lymphocytes. Hodgkin's paragranuloma has a much better prognosis than does Hodgkin's disease, and the patient may survive for many years. Eventually, however, the disease recurs, usually in a more malignant form. In the present case, for instance, the lymph node excised in 1962 showed the classic features of Hodgkin's disease. The cytology was much more pleomorphic, and Dorothy Reed cells, lymphocytes, and eosinophils were all seen.

DR. WHITAKER: We must now consider the cerebral symptoms. It is a striking fact that there were no abnormal signs referable to the central nervous system. On these grounds I think that we may exclude immediately such nervous diseases as multiple sclerosis. I wish that I could exclude a brain tumor with the same degree of confidence. I note that his vision was greatly impaired and that, although his fundi appeared in the main to be normal, there was slight edema of the central area. Did he have papilledema? Were visual fields studied? I should like to exclude a space-occupying lesion such as a localized mass in the region of the optic chiasma producing a raised intracranial pressure and hence papilledema and a bitemporal hemianopia.

DR. FITZGERALD: I examined the fundi. He had slight edema of the macula but no papilledema. Lumbar puncture was performed and the cerebrospinal fluid pressure was normal. The results of analysis of the cerebrospinal fluid were: sugar, 63 mg. per cent; protein, 33 mg. per cent; and chloride, 725 mg. per cent. He had no clinical signs of a raised intracranial pressure such as headache, vomiting, and bradycardia. Here are the visual fields.

DR. WHITAKER: Well, these do in fact show a bitemporal hemianopia. I should like to see radiographs of the chest and skull; one must always be on the lookout for cerebral metastases from a primary chest lesion. (These were shown.) Well, both are normal. I must conclude from all these investigations that we must look elsewhere for an explanation of the cerebral symptoms.

Returning to the clinical story, we find that all the important signs are referable to the arteries which supply the head and



Fig. 1. Lymph node showing Hodgkin's paragranuloma. [illegible] and eosin. ×250.



Fig. 2 Angiogram showing arch of aorta and its [illegible] branches. Only the origins of the great vessels fill normally (for details see text). The vessels [illegible] in the neck [illegible] vertebral artery.

neck and upper limbs. Note the weak or absent pulses in the superficial temporal and carotid arteries and the weak pulse in the left radial artery. We are told that the blood pressure was unobtainable in the left arm. Note, however, that the femoral pulses were obtainable and that the blood pressure in the lower limbs was normal. All these signs, together with the murmurs suggestive of obstructed and collateral blood vessels, lead me to believe that this patient had obstruction of the branches of the aorta with resultant ischemia of the midbrain. If we regard his visual impairment as tubular vision it would fit in very well with this diagnosis. I should like to see the results of an angiogram on this patient. I presume you do these at Birmingham! (These were shown.) Well, there you are. Obvious narrowing of several branches of the aortic arch!

DR. HEATH: The left subclavian artery is totally occluded just beyond the origin of the left vertebral and thyrocervical branches (Fig. 2). The radiologist reported that there was a very poor collateral reentry from the latter and from the suprascapular and lateral thoracic vessels. The left axillary artery filled only at a late stage. The origins of both vertebral arteries are very narrow, the left one more so. Both carotid arteries are very narrow, the right one from its origin upward and the left one tapering down in the lower neck. Both carotid arteries dwindle to nothing as they proceed up the neck. Views of the skull show the vertebral arteries to be entirely responsible for the intracranial circulation. The right subclavian artery is narrowed over a distance of 1½ inches beyond the origin of the internal mammary artery. You would accept all these findings as confirming your clinical impression? If so, would you care to give this syndrome a name?

DR. WHITAKER: Yes, these findings all confirm my view that this young man's symptoms were due to widespread occlusion of the branches of the aortic arch with ischemia of the brain. As for a name, I could call it *pulseless disease* or *Takayasu's syndrome* if you like. The only trouble with employing a term such as this is that it implies that one knows what



Fig. 3 Aorta. There [illegible] intimal [illegible] thinning and disrupt[illegible] of the [illegible] stain (C [illegible] X 7[illegible])



Fig. 4. Aorta. The fibrous intima is seen above. Below is the media showing broken-up elastic laminae. Elastic van Gieson ×100.

one is talking about, which is not the case. We still have to consider what the vascular disease present was and whether it was related to Hodgkin's disease. I suppose that one could postulate that the vascular occlusion had been brought about by the pressure exerted on the vessels by enlarged lymph nodes. But such a situation would be unique, and I do not believe that it happened. Did he have syphilitic disease of his aorta and its branches? What was the result of the Wassermann reaction?

DR. HEATH: It was negative.

DR. ABER: He had considerable x radiation to his neck. Did he develop radiation fibrosis of his arteries?

DR. WHITAKER: I do not think so, because we are told pointedly that his left radial pulse was impalpable at the beginning of his illness, before his course of radiotherapy began.

MR. WHITTLE (student): Could he have developed a fungal infection of his arteries secondary to the effects of radiation or the reticulosis?

DR. BREWER: The same objection applies. At the outset it was noted that there was an absence of pulse in the left radial artery.

Well, in fact, at autopsy this patient was found to have had a chronic fibrosing arteritis affecting the aorta. The aorta was normal to the level of the renal arteries, but between these vessels and the aortic bifurcation the intima was white and thickened with fine closely set transverse wrinkles. Histologically, the intima was thickened by acellular fibrous tissue (Fig. 3). The elastic laminae of the media showed a widespread fine disruption (Fig. 4). No significant inflammatory exudate was present. The other arteries affected were the innominate, right and left common carotids, and right and left subclavians. In all these blood vessels there was substantial narrowing of the lumen due to acellular intimal fibrosis (Fig. 5). There was also considerable fibrous thickening of the adventitia. I am not sure what these changes signify. Several possibilities have to be taken into account. First, is it syphilitic arteritis? The anatomic distribution and the histologic appearances are very much against this, and the patient is really too young. Furthermore, the Wassermann reaction is negative. We are familiar



Fig. 5. Left subclavian artery showing extreme fibrous thickening of the intima. The media is well preserved. Elastic van Gieson ×100.

with rheumatoid aortitis and arteritis[1] but there is no evidence whatsoever that this patient had rheumatoid disease. In my opinion the histologic appearances rule out giant cell arteritis. We can also discard the idea that his arterial disease was due to post-radiation fibrosis since the fibrosis occurred also in the lower abdominal aorta which was not exposed to such radiation.

We are left then with a residuum of rather ill understood and poorly described conditions. Among these are Takayashu's disease,[2] mentioned by Dr Whitaker. In this condition there is chronic fibrous obstruction of the main branches of the aortic arch. It is said to be common in Japan but this may be only because Takayashu was Japanese! This disease affects predominantly young women. Some of the patients have shown signs and symptoms exhibited by the patient whose case we have been discussing. But we must remember that syphilitic aortitis, atheroma and dissecting aneurysm may all produce an identical clinical picture. Recently rather similar changes have also been described in young Africans. Cases in which the anatomic distribution was similar, that is involving the lower end of the aorta and the great arteries of the neck, have been described in Japan. The only demonstrable lesions in the brain resulting from the vascular disease in this case was a recent softening in the brain 4 by 2 cm in area involving the left pre-Rolandic cortex and extending down into the underlying white matter for about 4 cm.

PROF. ORR: Is it not possible that this might be a case of giant cell arteritis of long standing in which fibrosis had altered the typical picture?

DR BREWER: It is possible but unlikely. He was young and giant cell arteritis is a disease of the elderly.

DR SMITH: What were the intracranial arteries like?

DR BREWER: They were normal.

DR FITZGERALD: I should like to point out that although Takayashu described in 1908 the disease which bears his name, a case of identical pathology and clinical features was described by Savory[4] in 1856.

STUDENT: What was the basis for the machinery murmur?



Fig. 6. Radiograph of chest showing diffuse miliary mottling.

DR WHITAKER: Blockage of branches of the aortic arch may give rise to systolic, diastolic or continuous murmurs. A localized block in a single artery will not give rise to a continuous murmur. The collateral supply is so good that there is no diastolic gradient. However, if there is extensive blockage of vessels there is a gradient across the block in both systole and diastole and hence a diastolic murmur.

DR HICKEY: What was the nature of the terminal illness?

DR WHITAKER: All the signs suggest a terminal bronchopneumonia. May I see a radiograph of the chest taken at that time? (This was shown—Fig. 6.) Well, this puts a different complexion on it altogether because the lung fields show a diffuse miliary mottling with a high left diaphragm which is probably paralyzed. There is also an opacity at the base of the left lung. Well, this could be a diffuse mottling due to the reticulosis or even miliary tuberculosis although I think that the latter possibility is unlikely.

PROF. ARNOTT: This is a very important card to be thrown on the table at this late stage of the proceedings. Certainly tuberculosis may cause arteritis. Were any tests for this disease made specifically?

DR FITZGERALD: One specimen of sputum was examined and found to contain no tubercle bacilli.

PROF. ARNOTT: Well, in the face of those

striking radiologic appearances. I think that this is strong evidence against tuberculosis.

DR. ABER: I do not agree. Even though this one specimen did not contain tubercle bacilli, I still think that the radiograph is very suggestive of miliary tuberculosis.

DR. BREWER: Well, in fact, at autopsy there was bilateral tuberculous bronchopneumonia. There were extensive confluent areas of caseation at the apex of the right lung and at the base of the left lung. The paratracheal and subcarinal lymph nodes showed caseous tuberculous lymphadenitis. Histologic examination showed that the alveolar exudate contained enormous numbers of acid-fast bacilli. By chance the sections included a microscopic caseating tubercle extending through the wall of a pulmonary vein. There were small caseating tubercles in the liver, spleen, and kidneys. Interestingly enough, there was little evidence of Hodgkin's disease. For example, the spleen was enlarged (196 grams) but showed no evidence of Hodgkin's disease. The only enlarged lymph nodes which did not show caseation were the para-aortic. Microscopically, they showed severe fibrosis and a few multinucleated giant cells, but one could not have made a diagnosis of Hodgkin's disease.

DR. FITZGERALD: This terminal tuberculosis was no doubt related to the treatment he received. He received an antimitotic drug, chlorambucil, 5 mg. twice a day. Later he also received prednisone 10 mg. three times a day. This was continued for 5 months until his death.

DR. HEATH: Well, I think that we may summarize this case by saying that this young man became ill with Hodgkin's paragranuloma, which gradually underwent transition into Hodgkin's disease. He developed a chronic fibrosing arteritis of the branches of the aorta which gave rise to striking ocular and cerebral symptoms. We do not know what this disease was precisely, and in particular whether it was related to the reticulosis. However, we believe that it was similar to that condition usually referred to as Takayashu's disease. This young patient died from miliary tuberculosis which he developed while on prednisone therapy.

Diagnosis: Takayashu's syndrome; Hodgkin's disease.

We wish to thank Dr. J. M. Malins for allowing us to report this case.

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The electrocardiogram and vectorcardiogram in congenital heart disease

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With the advent of corrective open heart surgery the specific diagnosis of congenital cardiac defects is no longer of academic interest only but is needed in order to decide the best management of the patients. Refined diagnostic procedures such as angiocardiography, cardiac catheterization, and dye-dilution studies, although needed for the workup of a significant number of cases, are not available at the cardiologist's office. Electrocardiography and vectorcardiography constitute an inexpensive and helpful aid in the establishment of a specific diagnosis of congenital cardiac defects when correlated with the patient's history and physical examination.

It is the purpose of this paper to present the most striking findings in the electrocardiographic and vectorcardiographic study of congenital heart disease. This study is based upon our own experience as well as that of other investigators.

The diagnoses in our cases were confirmed unequivocally by cardiac catheterization, operation, and/or autopsy studies. All of our patients had a complete 12 lead electrocardiogram including standard limb, augmented unipolar, and precordial leads. The vectorcardiograms taken were registered using the Grishman's cube system and a Sanborn Viso Scope apparatus. The vectorcardiographic loop was modulated and interrupted 400 times per second.

Fig. 1 shows the distribution of the mean electrical axis of the QRS complex in the frontal plane in a number of frequent acyanotic congenital cardiovascular disorders. Examination of this diagram presents certain interesting findings worth noting. It is seen that atrial septal defect, pulmonary stenosis, and ventricular septal defect have a predominantly mean electrical right axis deviation. The ostium secundum atrial septal defect has a right axis or a normal axis from 0 to +90 degrees. The presence of an ostium secundum defect with a mean electrical axis from 0 to −180 degrees is seen only very rarely. Ostium primum defects characteristically have a left axis deviation. Although congenital aortic stenosis might lead to significant left ventricular hypertrophy, it practically never leads to an electrical axis beyond

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−30 degrees. Uncomplicated patent ductus arteriosus practically never leads to right axis deviation except when there has been a considerable increase in the pulmonary arterial pressure. The axis of the ventricular septal defect will be dependent to some extent upon the presence of either a right to left or left to right shunt.

Fig. 2 demonstrates the relative distribution of the mean electrical axis of the QRS complex in the frontal plane in cyanotic cases and allows certain interesting observations. The mean electrical axis in tricuspid atresia usually ranges from 0 to −120 degrees. The presence of a normal or right mean electrical axis in patients with tricuspid atresia is highly suggestive of an associated pulmonary atresia or transposition of the great vessels with large pulmonary arteries. In tetralogy of Fallot a characteristic right axis deviation ranging from +90 to −210 degrees is usually encountered but occasionally it may be located from −60 to +89 degrees. In Ebstein's malformation the mean electrical axis could be encountered in any of the six sextants although most frequently it was found from −60 to +180 degrees. The axis in single ventricle is most frequently located from +90 to +120 degrees and from −30 to −120 degrees. The axis in A-V communis is predominantly left from −30 to −150 degrees. The cyanotic conditions that have been reported with a left axis deviation of the mean electrical axis of the QRS in the frontal plane are tricuspid atresia, Ebstein's malformation, A-V communis, pentalogy of Fallot, te

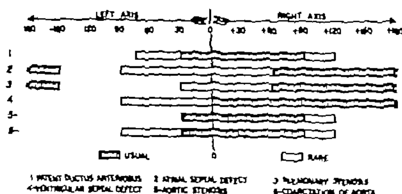


Fig. 1. The distribution of the mean electrical axis of the QRS in the frontal plane in 6 different acyanotic congenital cardiac defects.

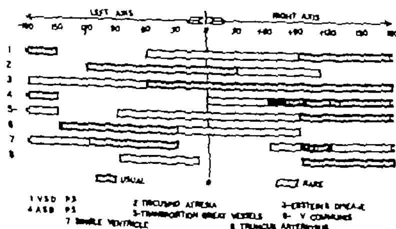


Fig. 2. The distribution of the mean electrical axis of the QRS in the frontal plane in 8 different cyanotic congenital cardiac defects.

trilogy of Fallot, Eisenmenger's complex, transposition of the great vessels, single ventricle, infantile coarctation, left atrial drainage of venae cavae, and trilogy of Fallot.

The classification shown in Table I lists the conditions that are likely to produce right ventricular hypertrophy, left ventricular hypertrophy, and biventricular hypertrophy or *diagnostic findings*. These are then divided according to the presence or absence of cyanosis. A further subdivision is made in regard to the presence or absence of systolic or diastolic overloading of the ventricles.

The following presentation consists of a summary of the most frequently encountered electrocardiographic and vectorcardiographic findings in different congenital cardiovascular defects according to the classification in Table I.

Atrial septal defect (secundum).[1,14] The mean electrical axis of the QRS is usually located between +60 and +210 degrees. The presence of left axis deviation is seen only rarely in the secundum type of defect and its presence is highly suggestive of ostium primum defect. The QRS configuration in Lead V_1 characteristically is of the rsR', rSr', or rSR' type. This occurs in about 80 per cent of the patients. In some instances with very high ventricular pressures the configuration is of the R type in Lead V_1. An S wave is frequent and a q wave is rare to absent in Lead V_6.

The P wave is peaked in the standard limb leads and/or Lead V_1 or V_2 in 25 per cent of the cases. Diphasic P waves in Leads V_1 or V_2 with an initial peaking occurred in 46 per cent of our 26 cases. Atrial fibrillation occurred in 12 and flutter in 2 in a series of 84 patients with ostium secundum defects. Only 1 of our patients had atrial fibrillation.

*The VCG shows that the QRS-E horizontal loop has a RSR' type of configuration characterized by a centrifugal loop which runs counterclockwise and later at the point of maximal deflection the centripetal loop either makes a figure of eight returning to the right in a clockwise fashion or is inscribed in clockwise fashion anterior to the centrifugal limb. A terminal and preterminal delay directed forward and to the right are common features in

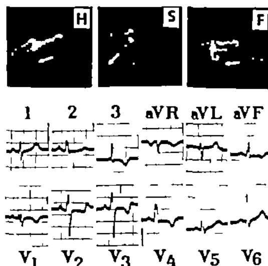


Fig. 3. Atrial septal defect of the secundum type. The electrocardiogram shows an axis of +90 degrees and a rsR'S complex in Lead V_1. An S is still present in Lead V_6. *In the VCG the horizontal loop shows counterclockwise rotation with terminal conduction delay. The sagittal lead shows anterior displacement of the QRS vector with terminal conduction defect.*

this entity. The T-E was directed downward, posteriorly, and to the left, opposite to the terminal delay in all cases.

The sagittal loop shows a mean QRS-E vector which fluctuates from 0 to +122 degrees and in 75 per cent of the cases there is a centrifugal limb which is inscribed downward in a clockwise fashion and a centripetal limb which makes a figure of eight moving upward counterclockwise and showing a terminal appendage directed anteriorly and superiorly. The T-E was directed opposite to the terminal appendage.

The frontal loop was inscribed clockwise in most instances and remained below the 0 to 180-degree axis. (See Fig. 3.)

Pulmonary stenosis.[13,14] *The electrocardiogram in pulmonary stenosis* with a small right ventricular pulmonary artery gradient might be normal. Otherwise there is right ventricular hypertrophy. There is a mean electrical axis of the QRS in the frontal plane from +60 to +210 degrees. In some instances it may fall from −30 to +59 degrees. In 65 per cent of our cases there was peaking of the P wave in the standard limb leads and in Lead V_1 or V_2. The QRS configuration in

Lead V_1 is mainly of the qR R or RS type pattern There is frequent slurring of the initial part of the upstroke of the QRS complex in Lead V_1 The R wave in the precordial leads on the right side may reach unusually high amplitudes

The vectorcardiogram in pulmonary stenosis may vary from an essentially normal one in mild stenosis to one showing a pattern of marked right ventricular hypertrophy All patients with moderate or severe stenosis show in the horizontal loop either a short counterclockwise efferent loop with an anteriorly inscribed larger afferent loop which returns in clockwise fashion to the isoelectric point or in severe pulmonary stenosis a more anteriorly displaced loop which runs clockwise along its entire course The TsE vector loop is progressively displaced more posteriorly as right ventricular pressure increases

The sagittal loop may show either a clockwise a counterclockwise or a figure of eight loop The loop is progressively displaced anteriorly and in some cases of very severe right ventricular hypertension the loop may rotate counterclockwise and will be located in the 0 to −90 degree quadrant The TsE vector will be located opposite to the main QRSsE vector in severe cases

The frontal loop will show a clockwise loop displaced to the right in all cases of moderate or severe pulmonary stenosis The mild type of pulmonary stenosis may have a figure of eight pattern with a counterclockwise clockwise loop or a counterclockwise loop (See Fig 4)

Tetralogy of Fallot [9-11] The main electrocardiographic features of this condition are the result of the hemodynamic burden upon the right side of the heart The mean electrical axis of the QRS in frontal plane is usually localized from +90 to +210 degrees Occasionally it might range from +90 to −60 degrees The most frequent QRS patterns in Lead V_1 are of the R Rs or qR type Initial slurring of the upstroke of the QRS complex in Lead V_1 is frequent Peaking of the P waves in Lead II has been reported in 28 per cent of the cases We had such findings in 17 of our 29 cases Characteristically these P waves are not of high amplitude

Table I

I Right ventricular hypertrophy
- A Noncyanotic
  - 1 Diastolic overloading
    - a Atrial septal defect with left to right shunt (secundum)
    - b Partial venous return to right atrium
  - 2 Systolic overloading
    - a Pure pulmonary stenosis
- B Cyanotic
  - 1 Diastolic overloading
    - a Total venous return to right atrium
  - 2 Systolic overloading
    - a Tetralogy of Fallot
    - b Eisenmenger complex
    - c Transposition of great vessels
    - d Pulmonary stenosis plus atrial septal defect with right-to-left shunt (trilogy)

II Left ventricular hypertrophy
- A Noncyanotic
  - 1 Diastolic overloading
    - Patent ductus arteriosus
    - b Ventricular septal defect
    - c Small aortic pulmonary defect
  - 2 Systolic overloading
    - a Aortic stenosis
    - b Subaortic stenosis
    - Coarctation of the aorta
- B Cyanotic
  - 1 Diastolic overloading
    - a Tricuspid atresia
    - b Single ventricle
    - Transposition of great vessels with ventricular septal defect

III Biventricular hypertrophy
- A Noncyanotic
  - 1 Left ventricular diastolic overloading plus right ventricular systolic overloading
    - a Ventricular septal defect with pulmonary hypertension
    - b Patent ductus arteriosus with pulmonary hypertension
    - c Truncus arteriosus with good pulmonary circulation
  - 2 Biventricular diastolic overloading
    - a Ostium primum defect
    - b Left ventricular-right atrial canal
- B Cyanotic
  - A V communis
  - b Transposition of great vessels with associated anomalies
  - Single ventricle
  - d Ebstein disease

IV Diagnostic electrocardiogram
- 1 Dextrocardia
- 2 Anomalous origin of left coronary artery

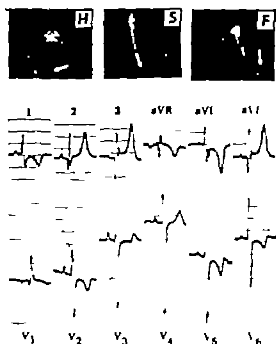


Fig. [illegible] Complete [illegible] position of the great [illegible]. The electrocardiogram shows Q waves [illegible] Lead II, III, and [illegible] inverted T in Lead I, aVL and [illegible] The T wave [illegible] Lead V[illegible] is upright. There is peaking of the T wave from Lead V[illegible] to Lead V[illegible] and there [illegible] R complex in Lead V[illegible]. The VCG [illegible] right ventricular hypertrophy.

case. In these cases marked pulmonary hypertension or hypertrophy of the outflow tract should be considered. The typical VCG features of right ventricular hypertrophy are seen.

Toscano Barbosa and Du Shane found that 15 per cent of their patients with ventricular septal defect displayed counterclockwise rotation of the QRS loop above the isoelectric line similar to that of patient with AV communis. (See Fig. 9.)

Aortic stenosis.[3] The electrocardiogram may be normal. In patients under 10 years of age this depends to some extent upon the peak systolic gradient. The mean electrical axis of the QRS in the frontal plane usually ranges from −30 to +90 degrees and is rarely encountered in the +90 to +120-degree range.

In patients with a significant hemodynamic burden upon the left ventricle definite evidence of left ventricular hypertrophy will be encountered. It is interesting to note that in spite of the left ventricular hypertrophy striking left axis shifts are not found. In those patients with left ventricular hypertrophy there is frequent T wave inversion from Lead V_4 to Lead V_6 and a qR pattern in these leads. In patients under 10 years of age severe obstruction has been found to be associated with T wave angles to the left of −40 degrees and QRS-T angles exceeding 100 degrees. (See Fig. 10.)

Coarctation of the aorta.[4,11] The electrocardiogram in coarctation of the aorta is either normal or representative of overwork of the left ventricle. The mean electrical axis of the QRS in the frontal plane usually ranges from −30 to +90 degrees and occasionally from −30 to −90 and from +90 to +120 degrees. Frequently there is left ventricular hypertrophy. It is manifested by tall R waves in Leads V_5 and V_6. In spite of the presence of left ventricular hypertrophy the mean electrical axis tends to be within normal range or is slightly deviated to the right. The QRS pattern in Lead V_1 is characteristi

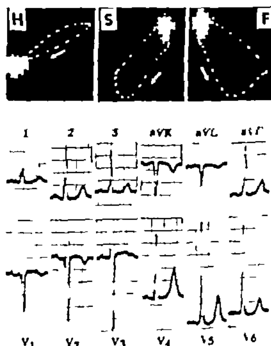


Fig. 8. [illegible] due to [illegible] of the [illegible]. The electrocardiogram shows [illegible] small Q waves [illegible] V[illegible] and V[illegible] and [illegible] in the [illegible] of the R in Lead V[illegible]. There is a [illegible]. The VCG shows a clockwise rotation of the horizontal loop with slow inscription characteristic of left bundle branch block.

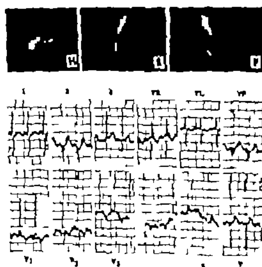


Fig. 9. Ventricular septal defect. The electrocardiogram shows right axis deviation, small peaked P waves in Leads II and V, right ventricular hypertrophy with initial slurring of the R in Lead V1 and deep S in Lead V. The VCG shows right ventricular hypertrophy.

cally of the rS type. Notched P waves in Lead II occurred in 50 per cent of our cases. (See Fig. 11.)

Single ventricle. There may be either right or left axis deviation with the highest incidence in the +90 to +120 degree and −30 to −120 degree groups. In a group of 24 patients 10 were found to have right ventricular hypertrophy with tall R waves in Lead V1 and deep S waves in Lead V6. Seven had left ventricular hypertrophy with deep S waves in Lead V1 and tall R waves in Lead V6. Two patients had entirely negative deflections in the precordial leads and 5 had signs suggestive of biventricular hypertrophy. High voltage complexes occurred in 33 per cent of the patients. Prominent P waves in Lead II occurred in 33 per cent of the patients. (See Fig. 12.)

Tricuspid atresia. The mean electrical axis of the QRS in the frontal plane ranges from +30 to −120 degrees. Whenever there is concurrent pulmonary atresia or transposition of the great vessels with large pulmonary arteries the mean electrical axis may fluctuate from normal to as much as +110 degrees. There is no documented case in the literature with an axis beyond +110 degrees. Tall prominent and sometimes notched P waves are frequent in Leads II and III. Diphasic or peaked P waves are frequent in Leads V1 and V. These P wave changes may occur as frequently as in 84 per cent of the cases. The QRS configuration in Lead V1 is of the rS type in most instances. A qR configuration in Lead V6 has been reported in 65 per cent of a series of patients. It occurred in all of our 7 patients. Left ventricular hypertrophy is frequent.

Supraventricular tachycardia including

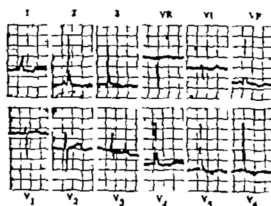


Fig. 10. Ventricular septal defect. The electrocardiogram shows small ... left ventricular hypertrophy.

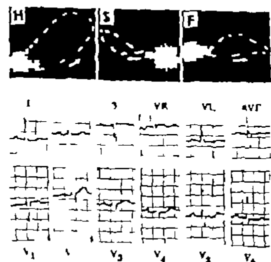


Fig. 11. Coarctation of aorta. The electrocardiogram shows left axis deviation, notched P waves in Leads I, II and V, and ... left ventricular hypertrophy. The VCG shows left ventricular hypertrophy.

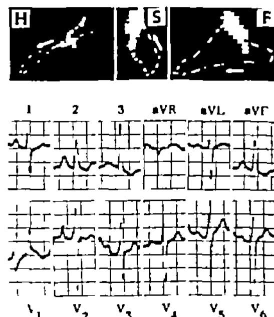


Fig 12 Single ventricle The electrocardiogram shows prominent tall and broad P waves in Lead II diphasic P waves in Lead V and tall peaked P waves in Lead V There is right axis deviation an rsR complex in Lead V and deep S in Lead V The VCG shows right ventricular hypertrophy

paroxysmal atrial tachycardia with variable A V block and left bundle branch block may occur in this condition Portillo encountered incomplete left bundle branch block in 5 of his 23 patients

The VCG of tricuspid atresia is characterized by large Q and R loops The R loop is displaced to the left posteriorly and upward and there is an early crossing of the centrifugal and centripetal branches with a clockwise rotation of the QRS-L loop in the horizontal plane Cabrera believes that it is improbable that a left bundle branch block is present because the Q loop is large and there is no increase in the duration of the QRS loop The A_{QRS} has ranged in the frontal plane from +60 to −100 degrees but usually these vectors are grouped between +30 to −16 degrees (See Fig 13)

Truncus arteriosus The mean electrical axis of the QRS complex in the frontal plane ranges from +90 to +180 degrees although occasionally it may range from −10 to −90 degrees The P waves in Lead II are usually peaked or notched The T wave is frequently inverted in Lead V and positive from Lead V to Lead V The QRS configuration in Lead V might be of the rsR R qR or RR type (See Fig 14)

A V communis There is a mean electrical axis of the QRS in the frontal plane ranging from −30 to −150 degrees In less than 10 per cent of the instances the axis may range from −30 to +90 degrees A first-degree A V block may occur in 18 to 40 per cent of the cases Frequently there is evidence of biventricular hypertrophy There is a predisposition to high voltage of the QRS complexes in all leads

Ostium primum defect The mean electrical axis of the QRS is deviated to the left in 90 per cent of the cases Prolongation of the P R interval is a frequent finding There is a tendency to biventricular hypertrophy

The vectorcardiographic pattern of ostium primum defects shows a counterclockwise upward rotation of the QRS loop in the sagittal lead and a counterclockwise rotation in the frontal loop which is usually located above the 0 to 180-degree axis The horizontal loop may be inscribed

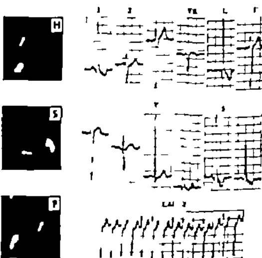


Fig 13 Tricuspid atresia The electrocardiogram shows left axis deviation a notched P wave in Lead V and left ventricular hypertrophy A strip of Lead II obtained when the patient had a supraventricular tachycardia is illustrated The VCG shows a clockwise rotation of the QRS loop in the horizontal plane the loop is displaced posteriorly and shows a delay in conduction This is typical of left bundle branch block

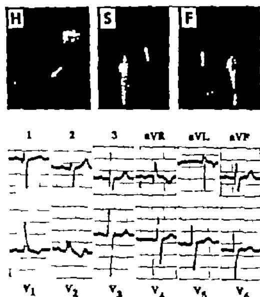


Fig 14 Truncus arteriosus The electrocardiogram shows right axis deviation an rR complex in Lead V[illegible] and deep S in Lead V[illegible] The sagittal lead of the VCG shows a counterclockwise-inscribed loop which [illegible] located in the 0 to 90-degree quadrant The frontal lead show a clockwise inscribed loop located in the 180 to −90 degree quadrant These findings are characteristic of right ventricular hypertrophy

clockwise or counterclockwise with a terminal delay The mean electrical axis as determined in the frontal loop is far to the left giving the well known left axis deviation in the electrocardiogram

Left ventricular–right atrial canal[26] We had 7 cases of this anomaly The electrocardiographic study in this group revealed a mean electrical axis of the QRS complex ranging from −68 to +54 degrees Peaked P waves occurred in Lead V1 in 4 cases notched P waves in Lead II in 2 cases and peaked P waves in Lead II in 2 cases An upright symmetrical T wave in Leads V4 and V[illegible] occurred in 6 cases and a Q wave in Lead V6 occurred in all patients Six of our patients had incomplete right bundle branch block Four had left ventricular hypertrophy and in the other 3 the tracings were suggestive of left ventricular hypertrophy

Vectorcardiograms were obtained in 3 of our 7 cases of left ventricular-right atrial canal The analysis of these 3 has revealed that the horizontal loop mean QRS-E vectors were +7 +30 and −10 degrees Two of these vectorcardiograms showed an anteriorly displaced centrifugal limb inscribed counterclockwise The terminal forces were displaced far to the right posteriorly and with a terminal delay The other vectorcardiogram showed a clockwise rotated loop in the horizontal plane This loop had a duration of less than 125 msec so that it did not fulfill the criteria for left bundle branch block

The sagittal loop mean QRS-E vectors for the 3 cases were +90 +90 and +110 degrees Two showed a clockwise inscribed loop with a posterior and superiorly located terminal appendage The other one had an initial centrifugal limb which was inscribed clockwise and then turned 180 degrees crossed clockwise the isoelectric point in a figure of eight and was displaced superiorly to return counterclockwise to the point of origin The T-E vectors were +130 +90 and 88 degrees

The frontal loops in the 3 cases had

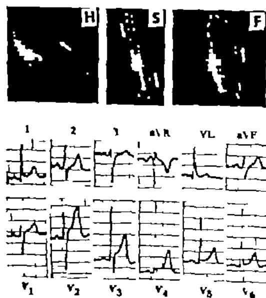


Fig 15 Left [illegible] ular right [illegible] There [illegible] left axis deviation [illegible] rS [illegible] in Lead V[illegible] tall R wave with rudimentary Q in Lead V[illegible] an upright T wave [illegible] in Lead V[illegible] Lead V6 The VCG shows in the sagittal loop [illegible] upward [illegible] posterior displacement of the QRS loop after an initial downward and clockwise inscription of the centrifugal limb These findings along with the counterclockwise and [illegible] upward displacement of the QRS loop in the frontal plane are reminiscent of the VCG of ostium primum

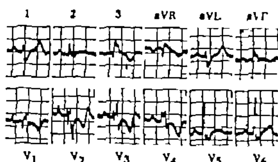


Fig. 16. Ebstein's disease. The electrocardiogram shows right axis deviation, first degree A-V block, peaked P waves in Lead V, small complexes with Q waves in Lead V and a broad S in Lead V.

QRS-I vectors of +55, +56 and −90 degrees. One vectorcardiogram showed a clockwise rotation and two had counterclockwise increased frontal loops.

The vectorcardiogram with the −90 degree mean QRS-I frontal loop also showed a terminal limb superiorly displaced in the sagittal plane. The vectorcardiogram is reminiscent of those described in cases of ostium primum defect. (See Fig. 15.)

Ebstein's disease.[14,3] The mean electrical axis of the QRS in the frontal plane is usually located from −60 to +180 degrees. There are reports of mean electrical axes in all the sextants. Prominent and peaked P waves in Leads II, III, V_1 and V_2 are frequently encountered. These are usually tall in comparison to the respective R waves. Some may attain a height of as much as 4 mm. Paroxysmal atrial tachycardia and atrial tachycardia with variable block and the Wolff-Parkinson-White syndrome are frequently encountered. The QRS complex in Lead V_1 and V frequently reveals a Q wave and tends to be of low voltage. Right bundle branch block occurs in 33 to 100 per cent of the cases.

The VCG shows that the P-E loop in Ebstein's anomaly is diphasic in about 80 per cent of the cases. The orientation of the initial limb of the P-E loop is inscribed downward, anteriorly and slightly to the left and the other terminal limb of P is displaced backward and to the left. In some cases the P loop is gigantic. The mean duration of the QRS-I loop was prolonged and in a large proportion of cases the horizontal loop showed an initial negativity with a clockwise inscription of the QRS-E loop. The B type of Wolff-Parkinson-White syndrome can be identified more frequently in the VCG than in the ECG. A terminal delay characteristic of a complete or an incomplete right bundle branch is also a frequent finding. (See Figs. 16 and 17.)

Corrected transposition of the great vessels.[12,13,18] The mean electrical axis of the QRS complex in the frontal plane was found to be localized from +90 to +120 degrees and from +30 to −110 degrees in a series of 29 cases.

An A-V block occurred in 18 of the 29 cases. Nine were first degree, 3 were 2:1 and 6 were A-V dissociation. There was frequently an initial Q wave in Lead V_1. Enlarged P waves in Lead II occurred in most cases and 12 of the 29 patients had upright T waves in all precordial leads.

Anomalous origin of the left coronary artery.[4] The presence of deep Q waves in Lead I, V_5 and V_6 in association with S-T changes and inverted T waves in a newborn infant is practically diagnostic of anomalous origin of the left coronary artery.



Fig. 17. VCG. Same patient with Ebstein's disease whose ECG is shown in Fig. 16. The horizontal loop shows right bundle branch block with a large anteriorly displaced E loop. The right bundle branch block and evidence of right atrial enlargement are seen in Ebstein's anomaly.

Summary

The highlights of the main electrocardiographic and vectorcardiographic features encountered in different congenital cardiac disorders have been presented. A modified classification of the congenital heart defects according to the main electrocardiographic findings and a distribution of the mean electrical axis of the QRS complex in the frontal plane of the electrocardiogram have been included.

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Alan F Lyon

Diuretic therapy

Part V Clinical use of thiazide diuretics

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All thiazides are rapidly and completely absorbed from the gastrointestinal tract. Peak levels in the blood are achieved at 2 hours after administration but peak diuretic effect occurs somewhat later. Differences between the members of the group in potency and in duration of action are generally related to their rate of excretion in the proximal tubule of the kidney where they are excreted unchanged.

There are wide variations both in activity and duration of action among different thiazides. Thus polythiazide, trichlormethiazide, and cyclothiazide are at least two hundred times as active by weight as the parent compound, chlorothiazide. The size of the dose is of little significance clinically. What is important is the diuretic effect of each compound at the maximum dose and the ratio between maximum therapeutic dose and the toxic dose. Despite the great differences in therapeutic dose there is little variation in maximum natriuresis produced by any of the compounds. The responses of individual patients vary much more than the responses to individual drugs. This general uniformity in effectiveness suggests that all the agents produce a maximal inhibition of the transport system involved and therefore it is unlikely that any new drug of the same group could be a more effective diuretic.

Moreover the increase in potency by weight has not led to any advantageous dissociation from side effects. Chronic loss of potassium with thiazides is because of the mechanism of its production (discussed previously) closely related to diuretic effectiveness. One would not expect and indeed one does not find any difference in chronic depletion of potassium. Furthermore increased potency by weight in the newer congeners has not resulted in any decrease in the incidence of hyperuricemia and hyperglycemia seen occasionally with all thiazides. As one would expect the less common idiosyncratic reactions occur independent of potency by weight. Thus skin reactions, nausea and vomiting, dizziness and paresthesias, pancreatitis, thrombocytopenic purpura, neutropenia and possibly photosensitivity and jaundice should be expected to occur with all members of the group.

Chlorothiazide when given intravenously shows beginning activity in 15 minutes, reaches its peak in 30 minutes and is no longer effective after 2 hours. Thiazides are rarely given intravenously because the mercurials are more effective

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by this route. The intravenous administration of chlorothiazide may be indicated when a patient is allergic to mercurials and oral administration would be difficult.

The action of chlorothiazide when given orally begins at 2 hours, reaches a peak at 4 hours, and lasts from 6 to 12 hours. At the other extreme is chlorthalidone. When a single oral dose of 100 mg. is given, the diuretic effect is noted first at 2 hours, reaches a peak at 18 hours, and lasts for 24 hours. If the maximal single effective dose of 200 mg. is given, natriuresis may persist for 48 hours. Polythiazide has been shown to have the same effect for 36 hours and methyclothiazide, quinethazone, and bendroflumethiazide for 24 hours. Hydrochlorothiazide, which shows maximal activity in 6 to 12 hours and has lost its effect after 18 hours, thus falls into an intermediate category. Because of these characteristics, some diuretics may be given for maximal effectiveness once a day rather than twice a day, and one, chlorthalidone, is fairly effective when given every 2 days. Nothing is gained by such schedules except convenience, inasmuch as the loss of potassium continues as long as the drugs cause diuresis.

Since continuous administration of thiazides may lead to hypokalemic alkalosis and other biochemical abnormalities, the dosage schedule chosen should be the smallest and most infrequent one that achieves the desired clinical effect. In states of retention of fluid, such as congestive failure, cirrhosis, and the nephrotic syndrome, the goal is to maintain the patient free of edema and comfortable. If this can be accomplished by a submaximal dose twice a week, this is clearly safer than a maximal daily schedule. Moreover, since restriction of the intake of salt is less hazardous than thiazide therapy, a higher than necessary dose of the drug should not be substituted for the maximum feasible restriction of salt.

The ideal dose of thiazide in hypertension is less certain. Although the use of thiazides alone has been shown in many individual subjects to produce a significant hypotensive effect, this effect has not been observed consistently. A recent large-scale cooperative double-blind study has suggested that thiazides alone are inadequate hypotensive drugs. Their value in potentiating the hypotensive effect of other drugs has been shown not only in small series but also in the same large cooperative double-blind study. Most clinical experience with thiazides in hypertension has been with doses close to the maximum and with continuous adminis-

Table I. Thiazide drugs and effective dosages

Generic name	Trade name(s)	Forms	Maximum effective dose
Chlorothiazide	Diuril	Tab. 250 and 500 mg. IV—500 mg. in 18 ml. of sterile water	1,000 mg. twice a day
Flumethiazide	Ademol	Tab. 250 and 500 mg.	1,000 mg. twice a day
Hydrochlorothiazide	Esidrix HydroDiuril Oretic	Tab. 25 and 50 mg. Tab. 25 and 50 mg. Tab. 25 and 50 mg.	100 mg. twice a day
Benzthiazide	Exna (formerly NaClex)	Tab. 50 mg.	100 mg. twice a day
Hydroflumethiazide	Saluron	Tab. 50 mg.	100 mg. twice a day
Chlorthalidone	Hygroton	Tab. 100 mg.	200 mg. once a day
Quinethazone	Hydromox	Tab. 50 mg.	200 mg. once a day
Bendroflumethiazide	Naturetin	Tab. 2.5 and 5.0 mg.	10 mg. once a day
Methyclothiazide	Enduron	Tab. 2.5 and 5.0 mg.	10 mg. once a day
Polythiazide	Renese	Tab. 1.0, 2.0, and 4.0 mg.	4 mg. twice a day
Trichlormethiazide	Metahydrin Naqua	Tab. 2.0 and 4.0 mg. Tab. 2.0 and 4.0 mg.	4 mg. twice a day 4 mg. twice a day
Cyclothiazide	Anhydron	Tab. 2.0 mg.	4 mg. twice a day

tration We know of no large scale well controlled study in which the dose of a thiazide necessary to produce a potentiating effect has been titrated In the absence of such information one cannot be sure that any dosage regimen that is much less than maximal is producing an effect

Table I lists the thiazide type of drugs that are or have been available the forms available and the maximum effective daily doses as reported in the literature

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Annotations

Thromboaortitis*

Most commonly, thromboobliterative disease of the aorta occurs in older persons as a consequence of atherosclerosis. The region of the bifurcation of the abdominal portion of the aorta is the site of predilection as described by Leriche. Obstruent aortic thrombi of similar pathogenesis may extend higher up in the abdominal segment producing syndromes associated with renal or mesenteric arterial occlusion. Although intimal atheromata appears to be the basic underlying defect, detailed histopathologic study of resected specimens in cases of aortoiliac occlusion has demonstrated a high incidence of focal or diffuse inflammatory changes in these [illegible]. The pathogenesis of these changes and their relationship to thrombosis is not known. Pepler and Simson[4] have described several [illegible] of thrombotic aortoiliac occlusion in adult Bantu males associated with nonspecific arteritis and little or no atherosclerosis.

Syphilitic aortitis, although declining in incidence, still accounts for the largest single group of aortic inflammatory lesions. Thrombosis of the aorta in syphilitic aortitis is for the most part limited to mural thrombus formation in saccular aortic aneurysm, which rarely compromises the lumen to a significant degree. The type of aortitis *most often accompanied by aortic thrombosis* is that associated with Takayasu's (pulseless) disease. Classically this is a chronic sclerosing panarteritis of young women which involves the aortic arch and/or the proximal segment of the brachiocephalic branches. It is characterized by marked excavation of all layers of the involved arteries and by dense bands of inflammatory cells in the media. Eventually the involved vessels assume the appearance of very thick-walled rigid tubes with marked narrowing or ultimate obliteration of the lumens due to superimposed thrombosis.

The etiology of Takayasu's arteritis is unknown. Certain authors have considered it to be a type of tuberculous angiitis, whereas some have postulated an allergic reaction to a tuberculous focus elsewhere in the body. However, others consider the disease to have a rheumatic or rheumatoid basis.[14] In either instance a hypersensitivity type of mesenchymal vascular response is seen as the underlying mechanism. The aortic lesions of Takayasu's disease can be readily distinguished from those of rheumatic or rheumatoid panaortitis. Although similarities exist, the latter disorders are characterized by severe intimal inflammation, microabscesses and focal fibrinoid necrosis, without significant mural thrombosis in the cases reported. Thrombotic occlusion of the aorta has not been described in rheumatic panaortitis.

Giant-cell or granulomatous arteritis is a widespread arterial disease which may involve the aorta. A relationship to Takayasu's disease has been suggested. In the aorta the lesions are confined largely to the media, and thrombosis, either mural or occlusive, is not a feature of this condition. It usually affects older persons, although a case has been reported in a 2 year old boy.

Several reports of idiopathic or unusual primary aortitis associated with renal artery occlusion and hypertension in children have been published.[20] In each case there was a segmental panarteritis of the abdominal aorta with superimposed mural thrombosis. In half of the cases there was also involvement of the thoracic portion of the aorta and in one instance the brachiocephalic branches were involved. In another recent communication Danaraj and co-workers[22] described 9 similar cases in young adults. It is probable that these cases represent *variants of Takayasu's arteritis*. Furthermore, additional reports of stenosing aortitis of unknown etiology[23] and acquired coarctation of the descending thoracic or abdominal aorta[24,25] are most likely examples of atypical pulseless disease which apparently has broader implication than originally suspected.

Coarctation of the aorta at the usual site is rarely complicated by thrombosis although further narrowing caused by concomitant calcific atheromatous degeneration may occur.[27] Congenital coarctation of the abdominal aorta is sometimes associated with occlusive mural thrombosis.[28] Aortic coarctation, however, not infrequently complicated by subacute bacterial endaortitis both at the constriction and at the site of the intimal jet lesion.[31]

Uncommon before the advent of antibiotics, pyogenic bacterial infections of the aorta in the absence of coarctation are now virtually unknown. These usually involved the aorta by extension from a bacterial endocarditis of the aortic valve or via the vasa vasorum from a para-aortic inflammatory focus.[32] Such invasions produced either subacute bacterial endaortitis or intramural abscesses of the aorta. Similarly, tuberculous aortitis was an un-

*This study was supported in part by [illegible] the Otto [illegible] Fund.

common complication by contiguity of pulmonary tuberculosis or para-aortic tuberculous lymph adenitis.[8,9] The formation of an aneurysm or rupture and mural thrombosis with secondary embolization are always hazards in such cases.

Primary acute aortitis comprises an exceedingly rare heterogeneous group of aortic inflammatory lesions in which the aortitis cannot be related either to endocarditis or to inflammation in an adjacent structure. These bacterial infections of the aorta are usually engrafted on a pre-existing aortic lesion which may contribute to the localization of the inflammatory process. In the cases described by Rappaport[36] and by Saphir and Cooper,[36] syphilitic aortitis was the underlying disease. Williams' case[37] was associated with idiopathic cystic medionecrosis and dissecting aneurysm of the aorta.

A case of primary acute panaortitis with thrombotic occlusion of the descending thoracic aorta in a 2-week-old infant has been reported recently. A bacterial origin for the aortitis could not be proved. Presumably, structural alterations in the aortic wall near the attachment of the ductus arteriosus predisposed to the localization, if not to the development, of the superimposed inflammatory process.

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Osmolar, electrolyte, and respiratory changes in hemorrhagic shock

If the term "shock" is confined to a condition associated with a low systemic arterial blood pressure, then the conditions can be separated into two main divisions. The first is hypotension associated with a normal or near normal blood volume, such as occurs in cardiac failure, neurogenic disorders, bacteremia (especially that due to *Bacterium coli* or staphylococci), impaired function of the suprarenal gland, and positive pressure ventilation wrongly applied with a mechanical ventilator. The second is hypotension associated with a low blood volume and implies either gross dehydration or loss of blood from the body or into closed cavities such as damaged muscle mass, the thorax, the abdominal cavity, or fracture sites.

The sum total of metabolic changes in each of these conditions is different, although the same biochemical changes may be seen in widely differing clinical circumstances.

In order to elucidate some of these findings, a number of dogs were anesthetized with hydroxydione[1] (21-hydroxy-pregnane-3,20-dione sodium hemisuccinate), allowed to breathe spontaneously, and bled into a reservoir containing approximately half the usual volume of acid-citrate-dextrose solution (A.C.D.) until the central aortic blood pressure was about 40 mm. Hg.[1,2] Great care was taken with the measurement of the blood pressure, since this is often ill defined in the literature. The period of hypotension was limited to 90 minutes, at the end of which time A.C.D. solution was added to the blood in the reservoir so that the proportion of A.C.D. solution to blood was the same as that used for transfusion in man. The total volume of blood lost, except that which had been taken for biochemical estimation, was returned to the animal. It was found that during the period of hypotension the animal suffered damage to the liver, kidneys, myocardium, and gut, particularly the terminal ileum, but irreversible hemorrhagic shock was not produced and the blood pressure reverted to normal values when the A.C.D. blood was returned to the animal. Of the 15 animals so treated, one survived for 10 days and another for 30 days, but damage to the kidneys and gut was present in both. During these experiments the following biochemical changes were noted.

The plasma sodium tended to fall and the plasma potassium and glucose to rise. The latter rose to high levels, e.g., 480 mg. per 100 ml., and this tended to offset the fall in plasma osmolarity resulting from the reduced plasma sodium concentration. A marked reduction in plasma total CO_2 (TCO_2) occurred; the lowest value recorded was 3.2 mMol. per liter in one of the 2 surviving animals. Hyperventilation reduced the carbon dioxide tension (PCO_2). All these observations have long been recognized. Claude Bernard, in 1877, noted the rise in blood sugar after hemorrhage, and Cannon, in 1918, was aware that a metabolic acidosis is produced.

Another 7 dogs were bled in the same way as the previous group, but during the period of hypotension they were infused with 2.74 per cent sodium bicarbonate solution.

The volume of 2.74 per cent sodium bicarbonate solution infused was calculated in order that the total body base deficit incurred over the whole period of hypotension was corrected. This volume was obtained by multiplying the total body water, which was assumed to be 60 per cent of the body weight, by 15, which was the mean base deficit in milliequivalents per liter produced in 5 dogs. This figure was multiplied by 3.07, the number of milliequivalents in 1 milliliter of solution. Bleeding was continued into a separate reservoir so that the same low blood pressure was maintained. In all but 4 cases only the blood lost before the infusion was returned to the animals. None of the animals treated in this way showed any signs of tissue damage in any organs. The first 4 animals had the blood that was lost before the infusion returned to them plus the blood lost during the infusion of sodium bicarbonate

solution in order to reduce the blood pressure to about 40 mm. Hg. In both stages of bleeding the blood was kept uncoagulated with the appropriate volume of A.C.D. solution. Two of these animals died from pulmonary edema. In all of the other animals which received infusions only the blood lost in the first stage of bleeding to produce hypotension was returned and although in some of the animals the blood pressure was a little below the prehemorrhage value this did not affect recovery. When sodium bicarbonate solution was infused the plasma TCO values rose to high level; the highest value recorded was 43.3 mMol per liter and pH values were similarly high, e.g. 66

Another group of animals was subjected to the same procedure but the animals were infused with 1.8 per cent saline which also has twice the osmolarity of plasma. These animals also suffered no tissue damage and survived just as easily even though no improvement in acid base state occurred. A third group of animals was infused with 10 per cent glucose and although this solution has twice the osmolarity of plasma only ? of 6 animals survived. Those animals that failed to survive had the typical changes of tissue damage. It is to be noted that the plasma osmolarity was not maintained at the same high level during infusions of 10 per cent glucose as during infusion of 1.8 per cent saline or ? 4 per cent sodium bicarbonate solution. When isotonic solutions were infused in an additional group of animals and the same volume of solution as in the previous groups of experiments was used, tissue damage still occurred during the hypotensive period and all the animals died. Increasing the volume of isotonic solution infused produced the same result.

In hot ... When hypotension resulting from hemorrhage extended over a period of 90 minutes a state of irreversible shock tended to appear generalized tissue changes occur and hemorrhagic necrosis may extend along the whole length of the small bowel.

When more than half the experiments had been performed an outbreak of enteritis occurred in the kennel and the animals died following the experiment after rapid tachycardia and a very high fever, the temperature of the heart being 44 C. The gut underwent damage along its entire length including the stomach and the colon. This was prevented by pretreating the animal for ... days with tetracycline. No antibiotics were given during or after the experiments and the antibiotic did not prevent the changes produced in the gut or elsewhere by hemorrhage in the control animal.

Thus it was concluded that because there was similarity ... the results from latter groups of animals treated with hypertonic electrolyte solutions ... osmolarity rather than acid base changes prevented tissue damage. This was supported by the fact that those animals which survived treatment with 10 per cent glucose solution maintained high plasma osmolarity because of raised plasma glucose concentration even though the plasma sodium fell markedly, e.g. to 111 mEq per liter, and also because isotonic solutions were ineffective in preventing tissue damage. In addition it was apparent that expansion of the extracellular fluid ... the ... factor.

Respiration The respiratory minute volume and rate were also measured and it was noted that spontaneous ventilation during the procedure was unaffected by acid base changes and that early termination of the experiment because of respiratory failure when the animals were infused with hypertonic solutions did not occur. When experiments were performed at a slightly higher central aortic blood pressure, e.g. above 60 mm. Hg in the central aorta, and the procedure extended until irreversible shock occurred, it was found that a marked fall in plasma osmolarity preceded this state and the onset of respiratory inadequacy. Thus from these experiments it is evident that hyperventilation does not result from the metabolic acidosis but from other physiologic phenomena. These may be the increase in the respiratory physiologic dead space which requires a more rapid alveolar gas exchange in order to maintain arterial blood oxygenation in the presence of an increased A-V difference and the increased importance of the thoracic pump in facilitating the venous return to the heart.

The results of these experiments imply that the treatment of hemorrhagic shock may have been oversimplified and that infection may have caused some confusion in experimental results since under certain conditions both contribute to tissue damage but in a different manner. Although the acid base state appeared to play little part in maintaining tissue integrity the importance of correcting a metabolic acidosis in the sick patient who may have experienced hemorrhage has already been stressed. The experiments supplied further evidence that infusion of sodium bicarbonate solution will not depress spontaneous ventilation by correction of the metabolic acidosis since a virtually equal increase in ventilation occurred in both the group infused with hypertonic saline and the group infused with hypertonic sodium bicarbonate. The mean increase in minute volume of the group infused with 1.8 per cent saline was 81 per cent and that of the group infused with 2 4 per cent sodium bicarbonate solution was 90 per cent. Although if the 2 animals which developed pulmonary edema are included this figure is reduced to 80 per cent.

It was concluded therefore that in the management of shock in man in addition to restoring blood volume it is necessary to hyperventilate in order to prevent hypoxia, to expand the volume and raise the osmolarity of the extracellular fluid space and to correct the metabolic acidosis. It may also be necessary to raise the blood sugar. In order to achieve this hypertonic solution should be infused. A suitable solution for this purpose was produced (See Table 1.) When this solution is used an excess of salt and marked fluid ... should not occur. It ... reasonable in view of the fact that

Table 1

NaHCO	1?? ml [illegible]	[illegible]	100	[illegible]
NaCl	?? ml [illegible]	[illegible]	100	[illegible]
Glucose	[illegible]	[illegible]	100	[illegible]
Osmolarity	[illegible]			

osmotic forces are potentially so enormous (plasma which has an osmolarity of approximately 300 mO mol per liter represents a force of 7.7 atmospheres or 5,800 mm Hg) that specialized cells such as those a part of the kidney and perhaps the liver and secretory layers of the gut may be vulnerable to rapid changes in the distribution of fluid and concentration of electrolytes

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Diagnosis of adhesive constrictive pericarditis

In our experience the diagnosis of constrictive pericarditis has often not been an easy one to make. Not only is it apt to be one of the last thought of by the clinician but even when it is suspected it is often difficult to persuade our medical and surgical colleagues that exploratory thoracotomy to make the diagnosis is justified on the evidence at hand. We have been impressed moreover by the relative ease with which the diagnosis was made in retrospect when proved cases were presented at clinical pathologic conference in contrast to the difficulty when the condition of the patient when first seen was an unsolved diagnostic problem. Evidently the diagnostic picture of this relatively uncommon ailment as conceived by the average physician did not fit very well the clinical syndrome presented by many of our patients. It occurred to us that a review and analysis of our proved cases might disclose enough common features to illuminate in some degree the diagnostic concept of this disease.

Fourteen surgically treated cases of constrictive pericarditis were found in the records of the teaching hospital of the Medical College of South Carolina for the past 17 years. The records were reviewed and the incidence of a number of findings considered to be of possible diagnostic significance was tabulated.

It was obvious that nearly all our patients had dyspnea, cough, distended neck veins, pleural effusion, cardiomegaly to some degree and hepatomegaly, whereas half had ascites and edema. All these are also features of congestive heart failure and offer little help in differentiating it from constrictive pericarditis. If these features are lumped together as congestive heart failure and others of high incidence but not common in congestive failure are added the most frequently appearing symptoms and findings in our cases were these:

Congestive heart failure in 13 cases, generalized nonspecific T wave changes in the electrocardiogram in 14, decreased cardiac pulsation by x-ray examination in 13 and fever as a prominent symptom in the development of the clinical picture in 12.

Although exact figures could not be determined it appeared that some cases were thought to be congestive heart failure of uncertain or varied etiology and were treated as such, sometimes with a considerable degree of success, before the correct diagnosis was eventually made. Other cases were at first considered most strongly to be collagen disease, polyarteritis or lymphoma. The diagnosis in every case was finally made when the attending physicians became suspicious enough to obtain a surgical biopsy of the pericardium.

Although a number of papers describing the many variations in the clinical picture of constrictive pericarditis have appeared, Beck's criteria[1] seem to have remained the most prominent in the mind of our clinicians as a minimum for diagnosis. Beck formulated the following triad for chronic compression: (1) increased venous pressure, (2) ascites and (3) a small quiet heart. As applied to our proved cases only one of Beck's criteria would apply significantly, increased venous pressure, which is seen just as commonly in congestive heart failure.

Criteria which would have been of much greater diagnostic applicability to our cases are these: (1) a picture of congestive heart failure with (2) generalized nonspecific T wave changes in the electrocardiogram, (3) decreased cardiac motion by x-ray examination and (4) fever as a prominent symptom at some time in the development of the disease. To have insisted on a small heart before

entertaining the diagnosis would have resulted in diagnostic error in the majority of our series since this feature was present in only 3 cases.

Pericardial biopsy was diagnostic in all of our cases and should be done if the four features mentioned above are present. This procedure in the hands of a present-day surgeon is rather benign and may be carried out under local anesthesia without seriously jeopardizing even severely ill patients. But we agree heartily with Hanlon[6] that "a high index of suspicion is the watchword in the diagnosis of adhesive constrictive pericarditis. The protean character of its manifestations seems to be the obstacle in arriving at a diagnosis."

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The sensitivity of insects to sexual olfactory stimuli

Insects possess well-developed chemical senses. Unlike the vertebrates, their sense organs for the chemical modalities are located at the body surface which is not covered by mucus and which is readily accessible to the surrounding medium. It is chiefly by these senses that most insects find their food, their mates, and food for their offspring, and that the social insects are enabled to make the manifold sensory discriminations necessitated by their highly complex social organizations.

Probably the most highly developed of the chemical senses of insects is that of smell (olfaction), and its prime use is the detection by one sex of the other for purposes of mating. The key to the survival of insects is their high reproductive potential, which depends on the ability of opposite sexes to find each other and mate. An important, if not essential, link in this process is the sex attractant, usually released by the female to lure the male. These chemical messengers have been called "ectohormones," and "sex pheromones," from the Greek pherein (to carry) and hormaein (to excite, stimulate). Whatever the term used, the potency of these materials is almost fantastic: infinitesimal amounts lure males from a distance depending upon the conditions present.[1] For example, one caged virgin female introduced into an area (*D. prionotes*) attracted well over 11,000 males in the field. The pure sex attractant produced by the female gypsy moth (*Porthetria dispar*) will lure males upwind at 10 micrograms from a distance up to ¼ mile,[2] and only 10 micrograms of the female sex attractant of the American cockroach (*Periplaneta americana*) is needed to cause extreme sexual excitement in the male;[3] this amount is equivalent to only 30 molecules. Insect sex attractants are probably the most potent physiologically active compounds known today.

In the moths and butterflies the attractants are usually formed in the lateral glands (sacculi laterales) of the abdomen of the virgin female. The female is able to protrude and retract these glands and thus regulate the release of the attractant. In many other insects, such as the cockroach, the location of the producing gland has not been determined. The scent of the sex attractants of the lepidopterous insects (moths and butterflies) and probably that of other insect orders is perceived by the male by means of olfactory receptors located in the antennae. Removal of one male antenna does not prevent detection of the sex scent, but complete removal of both antennae or coating the antennae with a thin film of lacquer results in loss of such reception. The male antennae consist of many fine hairs covered with numerous sensory cells (sensilla). The sensilla are classified into 15 main groups, of which the sensilla basiconica seem to be responsible for chemoreception. This method of reception is the basis of an extremely sensitive electrophysiologic method for the bioassay of insect sex attractants. By means of tiny silver chloride-coated silver electrodes inserted into the sensory hairs of the male antenna, it was found that a local electrical potential is set up by exposure to the female scent; the released nerve impulses are amplified and recorded from an oscilloscope to give characteristic

patterns called electroantennograms (EAGs). The shape of the patterns which depend on the stimulus is reproducible. Although most of the olfactory cells show signals (spontaneous frequency) preceding stimulation the EAG elicited by an attractant even in extremely low concentration is characteristic and unmistakable.

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Book reviews

THE ANATOMICAL LECTURES OF WILLIAM HARVEY Edited by Gweneth Whitteridge M A D Phil F S A Baltimore 1964 Williams & Wilkins Co 504 pages Price $20 50

This good book edited and translated by Gweneth Whitteridge is accurately defined by the title It is well documented by the use of footnotes which allows the reader to glance readily at the bottom of each page for references as he read along This book is a welcome addition to the medical literature even though the price high

AUSCULTATION OF THE HEART By Richard W D Turner OBE MA MD FRCP FRCPE Department of Medicine University of Edinburgh Second edition London 1964 E & S Livingstone Ltd 40 pages (U S A Williams & Wilkins Baltimore) Price $1 50

This 40 page pamphlet on auscultation of the heart a good summary of the teaching ideas and techniques of Turner A small bound booklet it will fit conveniently into a student pocket so that he may refer to it readily at any moment Although incomplete this booklet useful and worth its cost

ADVANCES IN CARDIOPULMONARY DISEASES VOL II Edited by Andrew L Banyai MD FCCP Clinical Professor of Medicine Marquette University and Burgess L Gordon MD FCCP Visiting Professor of Medicine Jefferson Medical Center Milwaukee Wis Chicago 1964 Year Book Medical Publisher Inc 347 pages Price $12

Th book edited by Banyai and Gordon summarizes some of the recent advances in cardiopulmonary diseases The purpose of this type f publication self e ident Among the bjects discussed are clinical diagnosis of chronic bron chitis and emphysema selection of antibacterial therapy for pneumonia mechanics of b eathing alveolar ga exchange sarcoidosis path logy of congenital heart disease and many others Some of the presentations are good and the book should be of alue to physicians and students even though the discussions are brief

A INDEX OF RORSCHACH RESPONSES STUDIES ON THE PSYCHOLOGICAL CHARACTERISTICS OF MEDICAL STUDENTS—I By Caroline Bedell Thomas Donald C Ross and Ellen S Freed Baltimore 1964 Johns Hopkins University Press 741 page Price $15

This is a massive nd probably unique olume The authors have been engaged in a study of the precursors of hypertension and coronary disease for the purpose of throwing light on the psychological physiological and genetic factors which may precede the development of these disorders nd the Rorschach test has been used extensively in the study A total of 1 154 subjects all medical students at Johns Hopkins University and of comparable intellectual capacity has been so tested since 1947 The effective evaluation of such large numbers of Rorschach record called for methodical organization of the responses Additionally t was considered that the result would be more meaningful if the interpretation could be given greater depth and breadth

Five hundred and eighty six young men and women of the total of 1 154 subject took the individual Rorschach test giving over 70 000 responses With the assistance of KWIC in devising a computer program which only recently became available the authors have retrieved from these data all of the significant words for each response to the 10 card in the Rorschach test and listed them alphabetically together with classifying information which establishes the context in which the word was given In addition to the Keyword Index an Area Index tabulates by number and other symbol the part of the inkblot that elicited the response and classifies the content Finally the Frequency Index l t the keyword and the number of times they were used in the responses

The bulk of the text consists of reproduction of the actual IBM tabulation types of Rorschach responses A brief introduction to the method reproductions of Beck s location charts as well as illustrations of some newl designated area and list of symbols complete the book

The authors have succeeded admirably in their attempt to make the Rorschach test results more scientifically productive It probable th t because of t pecial content nd al o its e the *Index* will be more properly a book for the university library or for a research g oup rather than a volume for the bookshelf of the ind idual reader However t should provide a basic reference guide to data on a group of superior adult for clinical and research p hologist psychiatrist and therapist

INDICATIONS AND TECHNIQUES IN ARTERIAL SURGERY Edited by Peter Martin V R D M Ch F R C S E F R C S Surgeon to Hammersmith nd Chalen ford Hospitals England Baltimore 1964 Williams & Wilkins Company 111 page Price $7 50

Th interesting book written by an experienced British vascular urgeon contains a great deal of useful information in its 111 pages The first three chapter by Ma or and Cockett on reconstructive operations in the aorto-iliac and femoral region are particularl good because of the exten experience of the author and the quality of accompanying illu trations Chapters concerned with carotid renal nd mesenteric

arterial obstruction suffer somewhat because of omission of the controversial aspects of indications for operation. In these regions, of course, such indications are complicated and deserve fuller discussion.

The material throughout the book is well presented, and many surgeons (including the reviewer) will agree with the authors in regard to indications for treatment and choice of operations, but the lack of a bibliography and the dogmatic approach to the subject will probably limit the distribution of this book considerably. Much of the material is now highly controversial, and *little purpose can be served by suggesting that these controversies have been resolved*. This book may be useful to surgical residents, but most practicing vascular surgeons are probably already thoroughly familiar with the concepts presented in it.

Announcements

The Czechoslovak Medical Society of J. E. Purkyně, Section of Surgery, in cooperation with the Czechoslovak Academy of Sciences and Slovak Academy of Sciences, is preparing an International Surgical Congress in Bratislava from June 28 to July 1, 1965.

The main topics of the program are: I. Surgery of Congenital Deformities; II. New Trends in Experimental Surgery. These will be discussed in the following sections: (1) general surgery, (2) cardiosurgery, (3) plastic surgery, (4) pediatric surgery, and (5) neurosurgery.

Surgeons from all countries are cordially invited to take an active part in the Congress. Participants are urged to submit their advance registration and title of lecture (twice) no later than Nov. 15, 1964, as well as a summary of the same in not more than 20 lines (3 copies) by Dec. 15, 1964.

Address all inquiries and information to: Administration Office of Surgical Congress, Doc. Ladislav Kuzel, M.D., C.Sc., Secretary General, Partizanska 2, Bratislava, Czechoslovakia.

The Sixth International Conference on Medical Electronics and Biological Engineering will be held on August 22-27, 1965, in Tokyo, Japan.

For additional information write to: Prof. K. Suhara, Secretary General, International Conference on Medical Electronics and Biological Engineering, c/o Japan Society of Medical Electronics and Biological Engineering, Old Toden Bldg., 1-1 Shiba Tamura-cho, Minato-ku, Tokyo, Japan.

The Second Annual Seminar in Cardiology, Diagnostic Methods in Cardiology, will be held at the Tampa General Hospital, Tampa, Fla., from Dec. 3-6, 1964.

The Seminar will be under the direction of Dr. H. J. L. Marriott, Director of the Cardiology Center, Tampa General Hospital, and the Faculty will include Dr. Agustin Castellanos, Jr., Miami; Dr. Frank LaCamera, St. Petersburg; Dr. Joseph K. Perloff, Washington; Dr. Gerold L. Schiebler, Gainesville; and Dr. Bernard Tabatznik, Baltimore.

Registration will be limited to 100.

For further details write to the Cardiology Center, Tampa General Hospital, Tampa, Florida 33606.

Clinical Pharmacology Training Program. The Division of Clinical Pharmacology, Departments of Internal Medicine and Pharmacology, State University of Iowa, offers a fellowship in clinical pharmacology to physicians with at least 1 year but preferably 2 years of house staff training in medicine or the equivalent.

The training program is designed for individuals interested in full-time academic, public service, or other scientific careers concerned with clinical pharmacology, and also for those physicians who primarily desire clinical training but wish to spend at least one additional year in basic sciences closely related to therapeutics. The first year is composed largely of training in basic pharmacology, with emphasis on biostatistics and experimental design. The second year of the program is devoted to the practical application of this knowledge in controlled clinical trials. Accepted candidates are enrolled in the Graduate College and receive courses in advanced pharmacology, biostatistics, experimental design, and related courses in the allied sciences. Co-directors are Dr. Walter M. Kirkendall and Dr. William R. Wilson of the Department of Internal Medicine and Dr. Lauren A. Woods of the Department of Pharmacology.

The beginning stipend is $6,000 per annum plus an allotment for dependents. Applications may now be filed for the year beginning July 1, 1965, and for the year beginning July 1, 1966.

Write to: Dr. Walter M. Kirkendall, Director, Cardiovascular Research Laboratories, State University of Iowa, Iowa City, Iowa.

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Editorial

Overweight and hypertension in emerging populations

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It is commonly thought that overweight and elevated blood pressure, although often outstanding features of the affluent society, are not serious health problems in primitive populations. It is important to recognize, however, that as these people come under the influence of western dietary habits and manner of life, the above-mentioned features are seen with increasing prominency.

Weight. Stamler[1] maintains that excess weight and the common American pattern of gain in weight from young adulthood into middle age are highly prevalent and highly serious risk factors from premature hypertensive and atherosclerotic cardiovascular diseases. The problem is not the severe, marked, huge circus type of obesity, but rather the 25 or 40 pounds put on gradually over the years—the moderate, creeping obesity so common among middle-aged American men. In one extensive study among insured persons, 20 and 23 per cent of the men and women, respectively, weighed 10 per cent or more than the average; moreover, 6 and 11 per cent of the men and women, respectively, weighed 20 per cent or more than average weight.

Certain primitive or less privileged populations gain little or no weight with age, e.g., indigent Indians,[3] African Samburu,[4] and Bushmen.[5] With the advent of urbanization and westernization, however, numerous changes are taking place.[6] We have found that with a rise in economic circumstances, Bantu girls, although not boys, attain skin folds which exceed in mean values those reported for corresponding White girls.[7,8] Among Bantu nurses and female teachers, both rural and urban, figures of mean *weight for height* are correspondingly excessive.[7] The same situation prevails in Johannesburg Bantu male teachers between the ages of 45 and 60 years.[11] In Durban, in an investigation on groups of urban Bantu, average weights of males and females between the ages of 20 and 64 years were given as 142 and 158 pounds, respectively;[9] corresponding fig

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[illegible] and other investigations on the [illegible] were supported by Grant No. [illegible] of the National Heart Institute, United States Public Health Service.
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ures for subjects studied by us in rural areas are 133 and 131 pounds.[7] Among urban Bantu pensioners between the ages 60 and 100 years (the most indigent of elderly Bantu) mean weights of groups of 50 males and 150 females were 145 and 165 pounds respectively.[7] There is ample evidence therefore concerning the proneness to excessive weight by the urban Bantu especially the females. The relatively sudden change from undernutrition to overnutrition which has occurred elsewhere as for example in Chile has also resulted in obesity being the main nutritional problem of adults.[10]

Blood pressure. In the United States according to Master and associates[11] from ages 40 through 64 years the blood pressure rises such that 22.7 to 38.7 and 18.0 to 39.3 per cent respectively of men and women have a diastolic pressure of 90 mm. Hg or more.

Some primitive or underdeveloped populations display little or no rise in blood pressure with age, e.g., indigent Indians,[8,12] African Samburu,[4] and Bushmen,[3] certain Australasian[13] and South American populations,[14] and Gilbertese.[15] Among rural Bantu mean pressures for age appear to be little different from those reported for White populations.[7,11,16] With urbanization however blood pressure tends to rise; in some groups the elevation is enormous. In one investigation on Zulu Bantu between the ages of 45 and 64 years the proportions with diastolic pressure of 90 mm. Hg or higher in a comparison of rural and urban areas rose from 26 to 44 per cent in the case of males and from 36 to 59 per cent in the case of females.[17] In the Transvaal we have noticed the same trend although to a less marked degree.[7] Blood pressures of Africans in West Africa are of much the same order as those of Whites[18]; the pressures reported for American Negroes (whose forebears came from West Africa) are far higher than those of U.S.A. Whites.[19] This phenomenon of rise in blood pressure with increasing westernization appears to be the usual response and has been reported from other parts of the world: India,[3] Easter Island,[4] New Zealand,[11] Russia. We have also observed this situation in a local emerging White population, namely

Poor Whites.[7,11] A recent study revealed that 50 women between the ages of 50 and 59 years had an average weight of 165 pounds and not less than 62 per cent had diastolic pressures of 90 mm. Hg or more.[7]

Effect of these changes on expectation of life. To what extent do these changes prejudice expectation of life in Whites? In some overweight groups according to Hutchinson the incidence of fatal heart disease is doubled, the incidence of vascular lesions of the central nervous system is significantly increased, the incidence of death from intrinsic renal disease is two and one half times the expected, and the incidence of deaths attributed to diabetes is increased by three and one half times. In the U.S.A. persons who are 25 per cent overweight are stated to have a decreased life expectancy of about 20 per cent. Thus at 40 years the expectancy of males, assuming it to be 32 years,[4] is shortened to 25½ years, i.e., by 6½ years. In regard to elevated blood pressure the handicap may be illustrated by the example given recently by Gill,[5] who referred to a 40 year old man with blood pressures of 135/90 mm. Hg. According to the 1959 Build and Blood Pressure Study of the Society of Actuaries,[6] males aged 40 years with the above mentioned pressures are exposed each year to a risk of death one and one half times as great as that of normal insured individuals. Gill indicates that the life expectancy of the man referred to is reduced by 4 years, i.e., from 32 to 28 years. The reduced expectations from overweight and from hypertension just mentioned may not seem to be inordinately large. Gill however has sought to put the situation in perspective by referring to cancer; he states that if deaths ascribable to malignant neoplasms were entirely eliminated it would increase the average span of insured males aged 40 years by only slightly over 2 years. Compare this with the 4 year reduction caused by a modest blood pressure elevation, namely, that of 135/90 mm. Hg cited.

The full bearing of the excessive overweight and hypertension on an emerging population such as the urban Bantu has not been studied and may not be known with certainty for some considerable time

Their present mortality from cerebral vascular disease is of the same order as that prevailing among the local White population [7, 8] but the mortality from hypertensive heart disease is far greater. It is well known that rates of mortality from these diseases in U.S.A. Negroes are far higher than among Whites [11, 5].

Primary influencing factors. What changes first with Whites have favored the occurrences of overweight and hypertension? There are many factors which are influential but perhaps the greatest relevant changes concern diet, activity and stress.

DIET. Less than a hundred years ago among Whites the diet was bulky and thus militated against overeating. Nowadays the latter is facilitated because most common foodstuffs are palatable, concentrated and highly digestible. In Britain a century ago the average daily consumption of bread made from lightly milled flour was about 600 grams per diem[30]; moreover among the poor a large amount of oatmeal porridge was eaten.[31] The consumption of bread now averages about 200 grams per diem.[4] The current daily consumption of sugar in Britain is about 150 grams,[4] which contrasts with the figure of 60 grams per diem consumed in Britain in 1881 [32] and less earlier in that century.[33] The present daily consumption of fat in Britain averages about 140 grams[4]; the figure was 80 grams in 1881 [32] and about 30 grams in 1835.[33] Undoubtedly similar although probably more marked changes have occurred in the United States. Yudkin[34] has emphasized one very important aspect accompanying these changes, namely, the present capacity to separate palatability from nutritional value. He maintains that palatability, which normally is a guide to nutritional value, is so no longer. The ability to separate sugar especially has been responsible for the vast increase in sugar consumption in the developed countries in the past 200 years and may well contribute to the increased incidence not only of obesity but also of coronary thrombosis and diabetes. Other dietary changes too may be relevant to the subject under discussion; thus Dahl and associate workers[35] have postulated that the high salt content of Western infants' diet (from cow's milk and proprietary foodstuffs) may have a relationship to hypertension in the adult.

ACTIVITY. This parameter too has changed tremendously. In bygone ages, as many as 19 out of 20 men were employed directly or indirectly in agriculture; at present in the United States only 1 worker in 20 is so employed. Even in occupations that are normally associated with activity, the actual amount of physical work carried out is decreasing on account of labor saving devices. Sport and athletic activities during school and college years are followed by relative inactivity thereafter. One important outcome of decreasing activity is that the appetite is no longer a reliable guide to nutritional need; eating to satiety often involves overeating.

STRESS. Before the industrial revolution, in some countries more so than in others, our forefathers in rural areas scarcely ever left the region in which they were born and although often poor and having numerous anxieties, they pursued their labors in the tranquil atmosphere depicted in Gray's Elegy in a Country Churchyard. Large families of 8 or more children were the rule. Nowadays the moving and uprooting of families are commonplace, their size is much smaller, competition is rife, and the acquiring of money and of status symbols are the cynosure of ambition. It is interesting, in passing, to note that blood pressure has been correlated with family size, parents with large families having the lower pressures[5]; also that noise and vibration have been correlated with increased hypertension.[11]

With determination some may regulate their diet, fewer their habitual activity, still fewer the stresses to which they are exposed. Yet without grossly altering the pattern of life, a reverse migration from urban to rural areas might be beneficial. Stamler and associates[1] have pointed out that the mortality rates from coronary and cerebral vascular diseases and hypertensive heart disease are far lower in rural Illinois than in Chicago.[11] A lower mortality from coronary heart disease in rural than in urban areas has also been noted in Britain.[4]

Changes in the above mentioned parameters, as already touched upon,[4] are being

encountered in increasing measure by emerging populations certain of whom are being exposed to a rapidity of urbanization far greater than that which occurred in the past with Whites. There is the progressive sophistication of diet and an increase in occupations that require mainly sedentary work. The regularity of *kraal* life in tribal communities, the production of large families—these are known to fewer and fewer Bantu as the trek to centers of population continues. Within the changing context of diet, activity, and stress, perhaps the most far reaching impediment to health is failure in adaptation. Scotch,[17] in his thoughtful study of sociocultural factors in the epidemiology of hypertension in the Zulu, has concluded that the individuals most likely to be hypertensive were those who maintained traditional cultural practices and who were thus unable to adapt successfully to the demands of urban living.

If, as Stamler[1] believes, a breakthrough against hypertensive and atherosclerotic disease is possible, then surely there is need to study overweight and hypertension and their ramifications much more comprehensively. Furthermore, the problems which beset emerging populations must certainly be given increased attention by such agencies as the Food and Agriculture Organization and the World Health Organization. Access by the Bantu and similarly placed populations to sufficient calories, with all the concomitant dietary and social changes, solves some health problems, but brings in its train others of greater complexity, ones with little likelihood of being overcome.

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Clinical communications

The medical ecology of public safety
I Sudden death due to coronary heart disease

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The progress of civilization has created for man occupations and avocations which would seem to make sudden and unexpected death a public health hazard. The automobile or truck driver on the multilaned highway, the aircraft pilot, the seaman steering a ship in a congested harbor—all would create a potential hazard for countless others if they were to die suddenly while performing their duties. This is especially true in an age of impatience when speed and its inherent dangers are the byword.

The most prevalent underlying cause of sudden and unexpected natural death is coronary heart disease[1-4] and it is therefore the disease that presents the greatest potential risk statistically. The purpose of this report is to present the results of an assessment of the magnitude of this public danger and to indicate what if anything should be done as preventive measures.

Materials and methods

The study consists of 1 348 instances of natural death due to coronary heart disease occurring in Dade County Florida between 1956 and 1962. Each death was sudden and unexpected and autopsy was performed by the staff of the Office of the Medical Examiner of Metropolitan Dade County Florida. Only instances in which death was clearly due to coronary heart disease (i.e. trauma did not play a significant role in the death of the patient) have been included. Any case without an autopsy was excluded from the study.

The term "sudden and unexpected death" as used herein refers to anything from instantaneous death to death an hour or two from the onset of terminal symptoms.

The diagnosis of fatal coronary heart disease includes any one or any combination of the following pathologic findings (1) hemorrhage into an atheromatous plaque causing occlusion of a coronary vessel (2) evidence of a recent myocardial infarction (3) presence of a fresh antemortem thrombus in a coronary artery (4) hemopericardium with cardiac tamponade secondary to rupture of the myocardium in the presence of a recent myocardial infarction and (5) presence of severe arteriosclerotic narrowing of the coronary vessels[1b] in a patient in whom no other major contributing causes of

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death were evident and whose past history and/or mode of death were consistent with coronary heart disease

The history of each patient was reviewed and past symptomatology was noted The occupation of each was obtained In addition the activity at the time of death any known avocations or hobbies age sex and race were recorded All of this information was obtained from a combination of the medical examiner's notes any available hospital charts the death certificate police records and the autopsy protocol Each case was placed in one of three major categories based on the medical history (1) previous known coronary heart disease (2) previous cardiovascular symptoms which were undiagnosed and (3) no previous symptoms

In cases in which undiagnosed symptoms had been known prior to death (category 2 above) the symptoms are broken down into three groups *classic cardiac symptoms* including typical anginal or coronary chest pains symptoms of congestive heart failure or symptoms of cardiac arrhythmias *atypical cardiac symptoms* including pain in the neck jaws or shoulders or gastrointestinal or other symptoms which in retrospect might have been due to coronary heart disease *other vascular symptoms* including symptoms and signs of peripheral arteriosclerosis such as intermittent claudication cerebrovascular symptoms and known elevated systolic blood pressure with mild or no elevation of the diastolic pressure

No lower age limit was used in the selection of cases however an upper age limit of 65 years was employed Persons over the age of 65 tend to be employed in less hazardous occupations and tend to avoid hazardous hobbies and avocations

The population and death rate statistics for Dade County were obtained from the Vital Statistics Report Section of the Annual Health Report of the Dade County Department of Public Health for the calendar years 1956 through 1962

Results

The total of 1 348 sudden and unexpected autopsied deaths due to coronary heart disease in persons 65 years of age and under represents an average of 21 4 deaths per 100 000 population annually for the 7 year period studied This is 7 8 per cent of the over all total annual incidence of deaths due to coronary heart disease (275 per 100 000 population per year) in Dade County (see Table I)

There were 1 040 (77 1 per cent) white males 170 (12 6 per cent) white females 98 (7 3 per cent) Negro males and 40 (3 0 per cent) Negro females among the 1 348 cases The age breakdown reveals that 10 persons between the ages of 20 and 29 years died unexpectedly of coronary heart disease 79 between the ages of 30 and 39 349 between the ages of 40 and 49 575 between the ages of 50 and 59 and 335 persons 60 through 65 years of age (see Table II)

Persons employed in public ground transportation (75 cases) constituted the majority of cases which would create a public hazard if sudden death were to occur while they were performing their duties (see Table III) In addition there were 13 seamen 8 airmen 17 electricians 4 police officers and 5 firemen

One hundred and one persons were engaged in terminal activities that were potentially hazardous to either themselves or others or both Fifty two (51 5 per cent) were driving private automobiles at the time of their death Fifteen were driving trucks and 4 were driving taxicabs Fourteen were in responsible or hazardous stations on board a ship or boat 10 were working at altitude 2 were piloting aircraft (one jet airliner and one light plane) and 2 were working on electrical circuits (See Table IV)

In the entire group of 1 348 cases 348 patients (25 8 per cent) had been known to have coronary heart disease prior to their sudden deaths 451 patients (33 4 per cent) had undiagnosed symptoms of cardiovascular disease (for which they may or may not have consulted a physician) and 549 patients (40 8 per cent) had no known symptoms whatever Of the 451 patients who were symptomatic but whose condition was undiagnosed 228 patients (50 6 per cent) had the classic cardiac symptoms described above 179 (39 7 per cent) had atypical cardiac symptoms and 44 (9 7 per cent) had other vascular symptoms

Table I Population and death rate statistics for Dade County Florida—1956 1962

Year	Population	Deaths	Death rate	Deaths due to coronary heart disease	Per cent of deaths due to coronary heart disease	Sudden coronary deaths in age groups 65 and under	Percent due to sudden coronary death (65 and under)	
							Per cent of total deaths	Per cent of coronary deaths
1956	734 142	6 668	9.1	2 046	30.68	132	2.0	6.5
1957	798 334	7 183	9.0	2 247	31.28	161	2.2	7.2
1958	847 185	7 989	9.4	448	30.64	198	2.5	8.1
1959	899 053	7 952	8.8	2 458	30.91	198	2.5	8.1
1960	930 394	8 243	8.7	2 537	30.78	243	2.9	9.6
1961	1 012 740	8 667	8.6	2 782	32.10	216	2.5	7.8
1962	1 079 176	9 172	8.5	2 889	31.50	200	2.2	6.9
Average 1956–1962	903 003	7 982	8.9	2 487	31.13	193	2.4	7.8

Death rate expressed in deaths per 1 000 population.

Occupations

TRUCK DRIVERS Thirty seven truck drivers died suddenly and unexpectedly from coronary heart disease during the 7 year period Thirteen of these men died while in their trucks In all instances either no accidents or only minor ones resulted and no other persons were injured in the cases in which accidents occurred Seven of the truck drivers had previously known coronary artery disease Seventeen had undiagnosed symptoms in 9 of whom they were of the classic cardiac type described above Thirteen had no cardiac symptoms whatever (see Table IV)

OTHER OCCUPATIONS INVOLVING THE USE OF PUBLIC ROADS Of a total of 32 drivers other than truck drivers there were 20 taxicab drivers 9 bus and streetcar operators 1 ambulance driver 1 private chauffeur and 1 automobile transport driver Five of these persons died at the wheel of their vehicle and two minor accidents occurred with no injuries to other persons or injuries contributing to the deaths of the subjects Ten persons had a previous history of coronary heart disease 14 had undiagnosed symptoms and 8 were completely asymptomatic

SEAMEN In this category which includes those persons with responsible or hazardous duty on board ship (i e yacht captains harbor pilots damage control men etc) there were 13 sudden deaths 5 of which occurred while the seaman was performing his duty No significant accidents occurred in this group although 2 of the patients fell overboard and had to be pulled from the water However this was not thought to be a factor contributing to death in either case Among the 5 who died on duty were 1 yacht captain 1 barge pilot and 3 ship s officers Only one of this group had a history of previous coronary heart disease 4 were symptomatic and 8 were asymptomatic

ELECTRICIANS Only 2 of the 17 electricians in the study were at work at the time of death Their illnesses caused no electrical accidents and they apparently did not get an electric shock themselves One was a lineman working on a high tension line and the other was working on an air-conditioning circuit box in a private home

AIRMEN Of the 8 professional airmen who died suddenly and unexpectedly 3 were airline pilots 1 was an airline flight engineer 1 was a commercial pilot and 3 were Air Force pilots The one professional airman who died in flight was a 48 year old pilot with direct but undiagnosed cardiac symptoms He died at the controls of a DC 8 jet airliner about 75

minutes after takeoff The aircraft was brought back safely by the remainder of the crew Although this was the only in flight death one other airline pilot did die of coronary heart disease a short time after landing

FIREMEN AND POLICEMEN None of the 5 firemen or the 4 policemen died while actively engaged in their work Only one in each of these groups had a previous history of coronary heart disease

RAILROAD ENGINEERS BRAKEMEN AND SWITCHMEN Six persons in this category died during the 7 year period 1 brakeman 2 switchmen and 3 locomotive engineers One of the engineers died while starting a locomotive but no accidents resulted Another died while the train was in motion but again no accident ensued

Terminal activities

DRIVING AUTOMOBILES Of 52 persons who died at the wheels of their private

Table II Age race and sex and previous cardiac status of 1 348 persons age 65 and under who died suddenly of coronary heart disease

Age (yr)	Race and sex	Previous history of coronary heart disease	Previous symptoms not diagnosed	No previous symptoms	Total
20–29	W–M	0	7	0	7
	W–F	0	1	0	1
	C–M	0	1	0	1
	C–F	1	0	0	1
	Subtotal	1	9	0	10
30–39	W–M	9	28	14	51
	W–F	2	3	2	7
	C–M	4	4	3	11
	C–F	3	5	2	10
	Subtotal	18	40	21	79
40–49	W–M	60	101	107	268
	W–F	6	12	11	29
	C–M	10	10	19	39
	C–F	2	9	2	13
	Subtotal	78	132	139	349
50–59	W–M	123	135	192	450
	W–F	17	24	30	71
	C–M	12	7	22	41
	C–F	6	3	4	13
	Subtotal	158	169	248	575
60–65	W–M	77	77	110	264
	W–F	13	23	6	62
	C–M	2	1	3	6
	C–F	1	0	2	3
	Subtotal	93	101	141	335
Subtotal	W–M	269	348	423	1 040
	W–F	38	63	69	170
	C–M	28	23	47	98
	C–F	13	17	10	40
Total		348	451	549	1 348

Table III Hazardous occupations by groups and specific duties

Occupational group	*Occupation*	*Number of sudden deaths*	*Per cent of hazardous occupation group*
Ground transportation	Truck drivers	37	30.3
	Taxi drivers	20	16.4
	Bus and streetcar operators	9	7.4
	Railroad locomotive engineers	3	2.5
	Railroad switchmen	2	1.6
	Railroad brakemen	1	0.8
	Ambulance drivers	1	0.8
	Private chauffeurs	1	0.8
	Auto-transport drivers	1	0.8
	Subtotal	75	61.4
Seamen	Barge and tugboat captains	4	3.3
	Officers on large ships	4	3.3
	Yacht captains	3	2.5
	Fire control men	1	0.8
	Damage control men	1	0.8
	Subtotal	13	10.7
Airmen	Airline transport pilots	3	2.5
	Air Force pilots	3	2.5
	Airline flight engineer	1	0.8
	Commercial pilots	1	0.8
	Subtotal	8	6.6
Electricians		17	13.9
Firemen		5	4.1
Policemen		4	3.3
Total	All hazardous occupations	122	100.0

automobiles 20 had known coronary heart disease 12 were symptomatic but their conditions were undiagnosed and 20 had no known symptoms (Table V) In 32 instances the fatally stricken driver was able to get his vehicle to the roadside and stop it without an accident* In 15 cases there were minor accidents involving property damage but no bodily injury Finally there were 5 cases of minor property damage and minor bodily injuries (not requiring hospitalization) There were no instances of major property damage or major bodily injuries or fatalities

DRIVING TRUCKS Fifteen men died while driving trucks (2 of whom were not truck drivers by occupation) with only two minor accidents (see *Occupations—Truck drivers*)

ON BOARD BOATS AND SHIPS Five of the 14 persons in this category were seamen performing their duties as described earlier 5 were seamen on board ship but not performing their duties at the time and 4 were persons in small pleasure craft No serious accidents or injuries occurred among this group

WORKING AT ALTITUDE Ten persons were in a precarious position above the ground when their terminal symptoms began Six of the 10 were on roofs 2 fell to the ground from one story 3 managed to get to the ground safely and 1 died on the roof The 3 who were on ladders also managed

*This includes instances in which the driver's wife grabbed the wheel and steered the car to the roadside.

to get to the ground before dying as did the one who was in a tree house.

PILOTING AIRCRAFT. There were two instances of pilots dying in flight in this series. One, the pilot of a DC 8 jet, has been described earlier. The other was a student pilot in a single-engine light plane. This 33-year-old man had had definite but undiagnosed cardiac symptoms for several months. He apparently became ill in flight and was not able to maneuver his craft to the ground. Witnesses saw the plane in straight and level flight about 150 feet above the surface before it suddenly dove straight down and crashed. Civil Aeronautics Board Investigators were able to identify no mechanical factors contributing to the crash, and postmortem examination revealed marked atheromatous occlusion of the coronary vessels and a fresh hemorrhage into an atheromatous plaque. Two other men in the series were known private pilots, but their deaths were not associated with flying.

DRIVING TAXICAB. See *Other occupations involving the use of public roads.*

OPERATING TRAINS. See *Railroad engineers, brakemen, and switchmen.*

WORKING ON ELECTRICAL CIRCUITS. See *Electricians.*

Discussion

The problem of the identification of the population creating the potential hazard is difficult. Only 25.8 per cent of the 1,348 instances of sudden and unexpected death occurred in patients with known coronary heart disease, whereas 40.8 per cent of the patients had no symptoms at all and 33.4 per cent had undiagnosed symptoms suggestive of coronary heart disease. The latter figure, representing premonitory symptoms of coronary heart disease, is within the ranges previously reported.[3,4] Over one half of this group with symptoms had the classic cardiac type described earlier. If both the patients with known coronary heart disease and those with classic symptoms of coronary disease were potentially identifiable in the general population, only 42.7 per cent of the 1,348 cases could have been subjected to any preventive measures that may have been thought to be desirable. However, this is unlikely, and it is more realistic to assume that only those with known coronary heart disease (25.8 per cent) could be reached.

Whereas previous studies of occupation and coronary heart disease have emphasized the possible effects of various types of work on the development of coronary heart disease,[9-11] the object of the current study was to assess the risk to the population at large created by sudden deaths due to coronary heart disease in persons 65 years of age and under who are engaged in hazardous occupations and activities. The primary practical question to be answered is: Does the magnitude of the risk warrant the development and application of specific preventive measures?

Physical standards for motor vehicle licensure have been suggested.[1,12] The results of the study indicate that the hazard created by sudden coronary deaths on public roads in the population studied is not very great (Table VI), and, therefore, the mere presence of coronary heart disease should not cause disqualification. These results agree with the previous findings of Peterson and Petty.[14] Most of those who died at the wheel of a motor vehicle managed to get to the roadside or at least avoid an accident before loss of consciousness or death. Therefore, despite the fact that seemingly adverse physiologic reactions have been demonstrated in drivers in both city traffic and high speed highway driving,[15] there does not seem to be justification for depriving coronary patients of the privilege of driving or, in the appropriate cases, of their means of livelihood solely on the basis of a very minor public hazard. However, certain specific exceptions to this generalization must be kept in mind—such as the school bus driver, the driver of a truck carrying explosives, etc. In these cases the public responsibility is extraordinary, and it would probably be wise to take no risk whatever. Furthermore, only 26 of the 71 persons who died while operating a motor vehicle had previously diagnosed coronary

*This case is classified as [illegible] death in the files of the Office of the Medical Examiner since it could not be [illegible] that the man [illegible] before the crash. However, the medical history [illegible] of the [illegible] and postmortem [illegible] strongly indicate that coronary disease was the [illegible] of the accident.

Table IV. Hazardous occupation groups compared to previous cardiac status

Occupation	Previous cardiac status	Age (yr.)					Sub-total	Total
		20-29	30-39	40-49	50-59	60-65		
Truck drivers	Known coronary disease	0	0	2	3	2	7	
	Symptoms not diagnosed	1	5	6	4	1	17	37
	No symptoms	0	0	10	3	0	13	
Taxi drivers	Known coronary disease	0	0	1	3	1	5	
	Symptoms not diagnosed	0	1	3	3	3	10	20
	No symptoms	0	0	1	1	3	5	
Seamen	Known coronary disease	0	0	0	1	0	1	
	Symptoms not diagnosed	0	0	2	2	0	4	13
	No symptoms	0	1	1	4	2	8	
Electricians	Known coronary disease	0	0	1	0	1	2	
	Symptoms not diagnosed	1	1	1	3	2	8	17
	No symptoms	0	0	3	2	2	7	
Pilots and other airmen	Known coronary disease	0	0	0	0	0	0	
	Symptoms not diagnosed	1	0	4	0	0	5	8
	No symptoms	0	0	3	0	0	3	
Firemen	Known coronary disease	0	0	0	1	0	1	
	Symptoms not diagnosed	1	0	2	0	0	3	5
	No symptoms	0	0	0	1	0	1	
Bus or streetcar operators	Known coronary disease	0	0	0	3	1	4	
	Symptoms not diagnosed	1	0	0	0	1	2	9
	No symptoms	0	0	1	1	1	3	
Policemen	Known coronary disease	0	0	0	0	1	1	
	Symptoms not diagnosed	0	1	1	1	0	3	4
	No symptoms	0	0	0	0	0	0	
Railroad engineers, brakemen, etc.	Known coronary disease	0	0	0	1	1	2	
	Symptoms not diagnosed	0	0	0	0	0	0	6
	No symptoms	0	0	0	4	0	4	
Other drivers (ambulance chauffeurs, etc.)	Known coronary disease	0	0	1	0	0	1	
	Symptoms not diagnosed	0	0	0	1	1	2	3
	No symptoms	0	0	0	0	0	0	
Subtotal	Known coronary disease	0	0	5	12	7	24	
	Symptoms not diagnosed	3	8	19	14	8	54	122
	No symptoms	0	1	19	16	8	44	
Total		5	9	43	42	23	122	122

heart disease, whereas 16 had undiagnosed symptoms and 29 had no known symptoms. Thus, at least 63 per cent of the persons who died suddenly at the wheel of a motor vehicle in this series would have been driving despite the existence of a law denying licensure to persons with a history of known coronary disease. Finally, a study of cases recorded as violent traffic deaths in which coronary heart disease was thought to be a significant factor in the fatal accident demonstrated that the public risk in this group was also relatively small.[18] In general, the question of whether the coronary patient should drive is best left to the judgment of his physician, who will

determine the answer on the basis of his evaluation of the capacity of the patient The individual's physiologic response to the disease rather than the mere anatomic presence of the disease should be used as the criterion The patient with frequent episodes of temporary cardiac incapacitation should be advised to refrain from driving

The problem of aviation privileges is somewhat different The pilot of an airplane cannot pull over to the side of the road as can the driver of a motor vehicle It is noteworthy that none of the 8 professional pilots and 3 private pilots in this study had a history of coronary heart disease—a reflection of the close following of the medical status of pilots by the Federal Aviation Agency and the United States Air Force and probably also of the younger age of this group Cases of attacks of coronary heart disease in flight do occur and are a true hazard both for the passengers and for persons on the ground below [17] Cases of coronary attacks in flight in which the pilots were able to land their aircraft before death have been reported [18,19] However the risk of a crash is great and every effort should be made on the part of physicians to rule out symp

Table V Hazardous terminal activities compared to previous cardiac status

Activity	Previous cardiac status	Age (yr.)					Subtotal	Total
		20–29	30–39	40–49	50–59	60–65		
Driving automobile	Known coronary disease	0	1	2	9	8	20	
	Symptoms not diagnosed	1	1	5	3	2	12	52
	No symptoms	0	2	6	8	4	20	
Driving truck	Known coronary disease	0	0	1	2	1	4	
	Symptoms not diagnosed	0	2	0	1	0	3	15
	No symptoms	0	0	5	3	0	8	
On board boat	Known coronary disease	0	0	1	2	0	3	
	Symptoms not diagnosed	0	0	1	3	0	4	14
	No symptoms	0	1	1	2	3	7	
Working at altitude	Known coronary disease	0	0	0	1	2	3	
	Symptoms not diagnosed	0	0	0	3	1	4	10
	No symptoms	0	0	2	1	0	3	
Driving taxi	Known coronary disease	0	0	0	2	0	2	
	Symptoms not diagnosed	0	0	0	1	0	1	4
	No symptoms	0	0	1	0	0	1	
Piloting aircraft	Known coronary disease	0	0	0	0	0	0	
	Symptoms not diagnosed	0	1	1	0	0	2	2
	No symptoms	0	0	0	0	0	0	
Operating train	Known coronary disease	0	0	0	0	0	0	
	Symptoms not diagnosed	0	0	0	0	0	0	2
	No symptoms	0	0	0	2	0	2	
Working on electrical circuit	Known coronary disease	0	0	1	0	0	1	
	Symptoms not diagnosed	0	0	0	1	0	1	2
	No symptoms	0	0	0	0	0	0	
Subtotal	Known coronary disease	0	1	5	16	11	33	
	Symptoms not diagnosed	1	4	7	12	3	27	101
	No symptoms	0	3	15	16	7	41	
Total		1	8	27	44	21	101	101

Table VI. Deaths while driving motor vehicles, with accident damage and injury rates

Prior cardiac status	No accident		Minor property damage, no injuries		Minor property damage, minor injuries		Major injuries		Fatalities		Total
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	
Previous known coronary disease	16	61.5	8	30.8	2	7.7	0	—	0	—	26
Previous symptoms not diagnosed	14	87.5	2	12.5	0	—	0	—	0	—	16
No previous symptoms	17	58.6	9	31.0	3	10.4	0	—	0	—	29
Total	47	66.2	19	26.8	5	7.0	0	—	0	—	71

toms of coronary heart disease in pilots. It may seem paradoxical, but in terms of public hazard the risk is probably greater when a private pilot or commercial pilot is involved than when an airline transport pilot is involved. Most airlines have in the cabin, in addition to the captain, two other pilots who are qualified to fly the particular aircraft. However, in a private plane or air taxi plane, there is in most instances only one pilot. The Federal Aviation Agency has begun the practice of requiring electrocardiograms on pilots with ATR (airline transport) ratings as a routine part of their medical examinations at age 35, and then annually beginning at 40 years of age.[28] Perhaps it would be wise to begin the same practice with private pilots (medical examination required every 2 years) and commercial pilots (medical examination required annually) even though the electrocardiogram leaves a great deal to be desired as a screening device.

Apparently, the problem with seamen is much the same as that with motorists, and no great danger to the public has been demonstrated. However, the cardiac patient on the small pleasure craft may present a special problem. These patients probably should be advised to carry another person on board who could handle the vessel in an emergency.

The other occupations and terminal activities studied do not present a significant public hazard, with the possible exception of the railroad engineers, brakemen, and switchmen. Here again, the safety of large numbers of people may rest in the hands of one man, and there is a responsibility to the public to keep risk factors down to a minimum.

Recent emphasis in the management of the postcoronary patient has been placed on vocational rehabilitation and a return to a degree of normalcy consistent with the functional capacity of the patient.[1, 3] With the possible general exception of aviation and certain specific exceptions in ground transportation, there does not appear to be justification to interfere with the activities or occupations of coronary patients on the basis of public hazard. Even the grounding of airline pilots who have a history of coronary heart disease may be open to question. Perhaps relegation of the airline captain to the position of co-pilot if he remains in Class I functional capacity and free of anginal attacks would be more justified than grounding him completely. However, Air Force and private and commercial civilian pilots (who are likely to be the only pilots in their respective aircraft) probably should be grounded.

Summary

A total of 1,348 instances of sudden and unexpected death due to coronary heart disease in persons 65 years of age and under in Dade County, Florida, was studied in order to determine the hazard to the general population created by these sudden deaths. Only 348 (25.8 per cent) of these

patients had had known coronary heart disease at the time of their death. There were 451 (33.4 per cent) instances of sudden death in patients with undiagnosed cardiovascular symptoms and 529 (40.8 per cent) cases in which there were no premonitory symptoms at all.

There were 122 persons (9.1 per cent of the total) whose occupations were potentially hazardous to the public. Twenty-eight of these persons were involved in their work at the time of their death with no serious accidents occurring as a result of their deaths.

One hundred and one persons (7.5 per cent) were involved in hazardous terminal activities at the time of their death. 52 of these were driving automobiles. Again no serious damage or injuries occurred.

The conclusion is that with certain specific exceptions there is at the present time no justification in interfering with the occupations or avocations of coronary patients on the basis of the hazard of sudden death which they present to the general population. Activities and work for these persons are best individualized for each patient on the basis of his functional capacity and symptomatology.

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Absence of Q waves in Leads I, aV_L, V_5, and V_6 in children

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The absence of Q waves in Leads I aV_L V_5 and V_6 has been described by Burch and DePasquale[1] as an electrocardiographic syndrome found in septal fibrosis They studied the hearts at 1 184 consecutive autopsies at the Veterans Administration Hospital in New Orleans Louisiana for the presence of septal fibrosis and correlated the results with premortem clinical findings and electrocardiograms All patients in the study were males At necropsy 142 (12 per cent) had septal fibrosis Of these all but one had coronary artery atherosclerosis 83 per cent had angina pectoris and 80 per cent had left ventricular hypertrophy Ages ranged between 38 and 84 years with a mean age of 63 years Fifteen were excluded from the study either because they had electrocardiographic changes of a bundle branch block which makes the determination of the presence or absence of Q waves in left ventricular leads tenuous or because no electrocardiograms were available Of the other 127 patients with septal fibrosis 80 per cent had no Q waves in Leads I aV_L V_5 and V_6 The patients without septal fibrosis at autopsy were used as a control group Of these 27 (2 per cent) demonstrated no Q waves in Leads I aV_L V_5 and V_6 Table I summarizes these data

Because of the common occurrence of atherosclerotic cardiovascular disease in the all male age group studied we wondered whether the absence of Q waves in Leads I aV_L V_5 and V_6 and the septal fibrosis found at autopsy were two unrelated coincidental findings To clarify this we studied the incidence of absence of Q waves in these leads in a different population

Methods

Electrocardiograms were taken on 408 unselected kindergarten and grade school children The children ranged in age from 4 to 13 years 219 (53 6 per cent) were females and 189 (46 4 per cent) were

Table I Summary of Burch and DePasquale s study of 1 184 cases

Septal fibrosis at autopsy	12%
Septal fibrosis no Q waves in Lead I aV_L V_5 and V_6	80%
Septal fibrosis Q present in Leads I aV_L V_5 and V_6	20%
Absence of Q in Leads I aV_L V_5 and V_6 but no septal fibrosis	2%

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Table II. Number of children according to age

Age (yr.)	Number
4	5
5	15
6	74
7	60
8	51
9	58
10	48
11	40
12	29
13	28

Table III. Summary of electrocardiographic findings in Leads I, aVL, V5, and V6 in 408 children studied

	Number	Percentage
Absence of Q waves	2	0.48
Embryonic Q waves	30	7.3
Q wave 0.4 mm. or greater	376	92.2

males. Table II shows the number of children according to age.

This population was chosen to eliminate the possibility of atherosclerotic cardiovascular disease and because of the large proportion of females. Younger children were not used in order to avoid normal right ventricular preponderance and because young children frequently fail to cooperate in the taking of electrocardiograms.

For a complex to have absolute absence of Q wave, there can be no initial downward deflection of the base line. Any suggestion of a Q wave disqualifies the electrocardiogram from the syndrome of septal fibrosis.

Results

Two of the 408 children (0.48 per cent) had an absence of Q waves in Leads I, aVL, V5, and V6. One was a female, the other a male. Thirty (7.3 per cent) had embryonic, often inconstant, Q waves measuring 0.1 mm. to 0.3 mm. in these leads. Of these, 17 were females and 13 were males. The electrocardiograms of the other 376 children demonstrated well-developed Q waves in the leads under discussion. All but 3 of the children studied had lost the juvenile pattern of right ventricular preponderance; however, none of these 3 demonstrated an absence of Q waves. Table III summarizes these data.

Discussion

In order to further evaluate the significance of an absence of Q waves in Leads I, aVL, V5, and V6, electrocardiograms of 408 unselected school children ranging in age from 4 to 13 years without known heart disease were studied. Of this group, 53.6 per cent were females. Only 2 (0.48 per cent) had an absolute absence of the Q waves in Leads I, aVL, V5, and V6 and could be considered as meeting the electrocardiographic criteria for septal fibrosis. Although the 2 children with absence of Q waves were apparently healthy, the microscopic state of their ventricular septa is unknown. In the children studied, the incidence of an absence of Q waves is far lower than the 2 per cent incidence reported by Burch in patients with microscopically normal septa. In at least one of these leads, 7.3 per cent of the children demonstrated Q waves measuring 0.1 mm. to 0.3 mm.

There seemed to be no relationship between QRS axis and the absence of Q waves in Leads I, aVL, V5, and V6. The two children without Q waves had axes of +60 and +75 degrees. Of the other 406 children, 1.2 per cent had a QRS axis of −30 to −50 degrees, 23 per cent had a QRS axis of 0 to +59 degrees, 58.5 per cent had a QRS axis of +60 to +90 degrees, 13.2 per cent had a QRS axis of +91 to +110 degrees, 1 per cent had a QRS axis greater than +110 degrees, and 0.5 per cent had a QRS axis that was indeterminate. The finding of an absence of Q waves in Leads I, aVL, V5, and V6 in only 0.48 per cent of the 408 children supports the concept that this pattern represents an electrocardiographic syndrome found in septal fibrosis.

Conclusion

The electrocardiograms of 408 unselected school children who ranged in age from 4 to 13 years, 53.6 per cent of whom were females, were studied for the presence or absence of Q waves in Leads I, aVL, V5, and

V_6. Only 0.48 per cent demonstrated an absolute absence of the Q waves in these leads. This supports and adds significance to the concept that absence of Q waves in Leads I, aV_L, V_5, and V_6 is an electrocardiographic syndrome found in septal fibrosis. No relationship between the QRS axis and this electrocardiographic pattern could be determined.

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The electrocardiogram in diphtheritic myocarditis

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Diphtheria remains as a constant menace[1]; sporadically, epidemics of the disease occur from populations in which the causative bacteria are endemic.[2] It has long been recognized that the electrocardiogram has an important place in the study of myocardial involvement because of the commonly associated conduction disturbances and ischemic type of changes. The intensity of the electrocardiographic abnormalities parallels in general the clinical severity of the disease. McCulloch[4] in 1920 observed 19 abnormal electrocardiograms in 80 consecutive cases of diphtheria. Abnormalities included inverted T waves, complete heart block, and bundle branch block. In 1921, Smith[5] reported that in 242 consecutive cases of diphtheria about 4 per cent of the patients developed a high grade heart block about the seventh day of the disease. The block was practically always of sudden onset and was followed by death in all patients within 48 hours in most cases. The severe prognosis of complete heart block was also recognized by Marvin and Buckley,[6] who reported 10 deaths in 11 cases. Mitchell[7] *reported 5 deaths in 8 cases,* and Begg[8] reported 8 deaths in 12 cases. Stecher[9] reported 19 cases of complete heart block in diphtheria, all with fatal termination. Bundle branch block was also an ominous sign,[4, 11] but Perry, Altschuler,[12] and Hoel and Berg[14] reported several cases with favorable outcome.

The earliest electrocardiographic abnormalities noted were depression of the S-T segment with decreased amplitude of T waves and later inversion in one or more of the standard leads.[15] Lepeschkin,[16] in a review of the literature, noted that the S-T shift was maximal in the first week after onset and was observed especially in Leads II and III and the left precordial leads.

In spite of the numerous reports available as to the incidence of and mortality associated with the various electrocardiographic abnormalities found in diphtheritic myocarditis, no attention has been given to the vectorial interpretation of these changes or to a method by which their intensity may be graded. This encouraged us to attempt to quantitate by an electro-vectorcardiographic interpretation sequential changes in tracings obtained in our series. When possible, these changes were related to clinical and pathologic states.

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and the severity of the disease processes particularly in patients with conduction disturbances

Material and method

volving the
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in which th
maximal def

to be normal. When this ECG sign was observed in association with physical signs of carditis, it was presumed to be due to the effects of diphtheria. Low amplitude of T waves without change in direction did not result in significant widening of the QRS-T angle. Contrariwise, it is well known that primary T wave changes, however prominent, are nonspecific and result from causes other than the effect of the diphtheria toxin. This point will be enlarged upon in the comment.

Results

In the total group of 229 children, 15 deaths resulted from diphtheria, all in the group of 47 patients who were found to have clinical signs of myocarditis. Ten fatalities were attributed to the myocarditis and peripheral circulatory failure. ECG abnormalities considered to be significant were present in these 47 patients and were arranged into four groups as summarized in Table I. No significant age differences were observed in these groups. Time relationships of ECG and clinical data were summarized for 8 patients upon whom autopsy was performed (Table VI).

A. Prolonged P-R interval. This group (Table II) comprised 11 patients with no ECG abnormality other than prolongation of the P-R interval. None developed congestive heart failure or received digitalis. The ECG sign was observed as early as 4 days and as late as 28 days, at a mean time of 9 days after the onset of the uniformly benign illness. The P-R interval had returned to normal in 5 patients after a mean duration of 4 months and had not subsided in the other 6 at a mean follow-up time of 13 months. All patients recovered.

B. Primary T wave abnormality. Two of the 13 patients in this group (Table III) also had a prolonged P-R interval. Three cases revealed pronounced S-T segment shift without concordant T wave changes. The widened QRS-T or QRS-ST angle, resulting mainly from a change in direction of the repolarization vector, was recorded as early as 3 days and as late as 2 months after initial symptoms of diphtheria, at a mean time of 20 days. The mean width of abnormal angles was 120 degrees. The angles regressed to within the limit of normal in all but 2 instances. No patients in this group developed congestive heart failure, and all recovered.

C. Intraventricular block. The group (Table IV) in which the QRS vector was shifted, but without widening of the pre-block or post-block value of QRS by more than 0.03 second, comprised 9 patients. The mean time of recording of the ECG abnormality after onset of the illness was 19 days; however, this time ranged from

Table I. ECG abnormalities in diphtheritic myocarditis

ECG abnormality	Number of cases	Mean age (yr.)	Mean observed time after onset of illness at which the ECG abnormality			Deaths
			Appeared	Subsided	Persisted*	
A. Prolonged P-R interval	11	7.0	9 days	4 mo. (5)	13 mo. (6)	0
B. Primary T wave changes	13	5.6	20 days	(11)	46 days (2)	0
C. Intraventricular block	9	6.0	19 days	4 mo. (4)	(5)	4
D. Major conduction block	14	6.0	12 days	30 days (6)	(8)	11

*Time of follow-up tracings [illegible]
Numbers in parentheses indicate the number of cases.

*Table II Prolonged P R interval**

Case	Age (yr)	Time of ECG after onset	QRS duration (sec)	QRS axis		T axis		QRS T spatial angle (degrees)	ECG diagnosis	Remarks
				Frontal (degrees)	Horizontal	Frontal (degrees)	Horizontal			
1	11	5 days	0 06	60	Pos	60	Pos	0	Normal	Recovery
		28 days	0 06	60	Pos	60	Pos	45	Prolonged P R	
		10 mo	0 07	60	Pos	60	Pos	0	Normal	
2	5	3 day	0 05	60	Lat	30	Lat	30	Normal	Recovery
		6 day	0 05	60	Lat	45	Pos	30	Prolonged P R	
		5 mo	0 06	60	Pos	60	Pos	0	Normal	
3	5	4 days	0 06	60	Pos	60	Pos	30	Normal	Recovery
		14 days	0 06	60	Lat	60	Lat	0	Prolonged P R	
		3 mo	0 07	60	Pos	60	Pos	0	Normal	
4	4	?	0 06	60	Lat	30	Lat	30	Normal	Recovery
		? + 5 days	0 06	60	Lat	30	Lat	30	Prolonged P R	
		? + 7 wk	0 06	60	Pos	30	Pos	30	Normal	
5	11	10 days	0 07	60	Lat	60	Lat	0	Prolonged P R	Recovery
		38 days	0 08	60	Pos	60	Pos	0	Normal	
6	5	6 days	0 06	80	Lat	100	Lat	20	Prolonged P R	Recovery
		3 yr	0 07	60	Lat	60	Pos	30	Prolonged P R	
7	4	4 days	0 07	60	Lat	60	Lat	0	Prolonged P R	Recovery
		2½ yr	0 07	60	Lat	60	Lat	0	Prolonged P R	
8	2	7 days	0 06	60	Lat	60	Lat	0	Prolonged P R	Recovery
		18 days	0 06	60	Lat	60	Pos	30	Prolonged P R	
		4 mo	0 06	60	Lat	60	Pos	30	Prolonged P R	
9	5	4 days	0 07	75	Pos	60	Pos	15	Prolonged P R	Recovery
		5 mo	0 07	75	Pos	60	Pos	15	Prolonged P R	
10	4	3 days	0 07	60	Pos	60	Pos	0	Normal	Recovery
		10 days	0 07	60	Pos	60	Pos	0	Prolonged P R	
		4 mo	0 07	60	Pos	60	Pos	0	Prolonged P R	
11	9	6 days	0 08	80	Pos	60	Lat	40	Prolonged P R	Recovery
		32 days	0 08	80	Pos	60	Lat	40	Prolonged P R	

*Prolonged P R interval was the most ... ECG ... of patients in Group A with reference to the times after onset of diphtheria. The columns labeled QRS ... and T ... Table II ... refer to the ... of ... and are indicated numerically in the frontal plane with reference to bipolar lead I and by P (posterior) ... (anterior) ... *Lat* (lateral) ... and *Sup* (superior) with reference to ... [illegible]

4 days to 2 months The mean width of the QRS when this ECG diagnosis was made was 0 083 second an average widening of 0 02 second of those tracings seen in this category before the block occurred

The ECG of one child (Case 27) revealed incomplete right bundle branch block observed only from the fifth to the eleventh days of a benign illness

The ECG diagnosis in the other 8 children was parietal block 4 of these children (Cases 30 33) died Case 30 an 11 year old boy with severe nasopharyngeal involvement died suddenly on the sixth day of illness presumably of shock Clinical and autopsy data are summarized in Table VI for Case 31 who died of airway obstruction and Case 33 who succumbed to

*Table III Wide QRS T angle due to primary T wave changes**

Case	Age (yr.)	Time of ECG after onset	QRS duration (sec.)	QRS axis		T axis		QRS T spatial angle (degrees)	ECG diagnosis	Remarks
				Frontal (degrees)	Horizontal	Frontal (degrees)	Horizontal			
12	3½	5 days	0 07	90	Ant	0	Po	90	Ischemia	Recovery
		11 days	0 07	75	Lat	0	Lat	60	Normal	
13	6	7 days	0 07	60	Lat	60	Lat	0	Ischemia	Recovery
								QRS-ST = 130		
		4 yr	0 07	60	Lat	60	Lat	0	Normal	
14	2/3	2 days	0 05	45	Ant	60	Pos	75	Ischemia	Recovery
		15 days	0 06	45	Ant	60	Pos	120	Ischemia	
		4 mo	0 05	45	Ant	60	Lat	30	Normal	
15	11	8 days	0 07	80	Pos	−30	Pos	75	Ischemia	Recovery
		9 days	0 07	80	Pos	60	Pos	20	Normal	
		8 mo	0 07	60	Pos	60	Pos	0	Normal	
16	9	3 wk.	0 07	60	Pos	−100	Ant	160	Ischemia	Recovery
		8 wk.	0 07	45	Pos	45	Pos	15	Normal	
		4 yr	0 08	60	Pos	60	Pos	0	Normal	
17	3	17 days	0 06	75	Lat	0	Pos	90	Ischemia	Recovery
		6 wk.	0 06	60	Pos	0	Lat	75	Ischemia	
18	5	2 mo	0 08	75	Pos	30	Lat	70	Ischemia	Recovery
		4 mo	0 07	75	Pos	30	Pos	40	Normal	
19	7	4 day	0 07	80	Lat	60	Pos	30	Normal	Recovery
		18 days	0 07	80	Lat	−60	Lat	140	Ischemia	
		51 days	0 08	80	Lat	0	Pos	90	Ischemia	
20	4	5 days	0 05	60	Lat	60	Lat	0	Normal	Recovery
		11 day	0 06	60	Lat	60	Lat	0	Nodal rhythm	
								QRS-ST = 180	Ischemia	
		2½ mo	0 06	60	Pos	60	Pos	0	Normal	
21	10	4 days	0 07	60	Po	60	Lat	30	Normal	Recovery
		11 days	0 0	60	Pos	30	Pos	70	Ischemia	
								QRS-ST = 135		
		31 day	0 07	60	Pos	30	Lat	60	Normal	
22	6	8 day	0 08	60	Lat	60	Lat	0	Prolonged P R	Recovery
		2½ mo	0 08	60	Lat	10	Pos	110	Ischemia	
		4 mo	0 08	60	Pos	60	Pos	30	Prolonged P R	
23	4	6 days	0 06	60	Pos	60	Lat	30	Normal	Recovery
		13 days	0 06	45	Pos	45	Lat	90	Prolonged P R	
		23 days	0 06	110	Lat	−120	Lat	150	Ischemia	
		2 mo	0 06	90	Inf	45	Pos	60	Normal	
24	4	3 day	0 07	60	Pos	150	Pos	90	Ischemia	Recovery
		4 mo	0 08	60	Pos	60	Pos	60	Normal	

*A widened QRS-T [illegible] the most [illegible] ECG ab[illegible] [illegible] of pati[illegible] Group B [illegible] the col[illegible] labeled *ECG d*[illegible] the term Ischemia refers to [illegible] QRS-T [illegible] QRS-ST spatial angles [illegible] described [illegible] the text

*Table IV Intraventricular conduction block**

Case	Age (yr)	Time of ECG after onset	QRS duration (sec)	QRS axis		T axis		QRS T spatial angle (degrees)	ECG diagnosis	Remarks
				Frontal (degrees)	Horizontal	Frontal (degrees)	Horizontal			
25	9	2 mo	0 08	−30	Pos	−90	Sup	90	Parietal block	Recovery
		2½ mo	0 08	−40	Pos	20	Lat	75	Parietal block	
		4 mo	0 08	−30	Lat	30	Lat	60	Parietal block	
26	7	6 days	0 07	−80	Sup	30	Lat	110	Parietal block	Recovery
		22 days	0 09	−80	Sup	30	Lat	110	Parietal block	
27	2	5 day	0 08	50	Ant	50	Pos	115	Incomplete right BBB	Recovery
		11 days	0 06	60	Lat	60	Lat	0	Normal	
		6 mo	0 06	60	Lat	60	Lat	0	Normal	
28	3	20 days	0 08	−60	Pos	170	Ant	140	Parietal block	Recovery
		11 mo	0 07	−75	Lat	30	Pos	110	Parietal block	
29	5	6 wk	0 07	−45	Pos	150	Pos	180	(Parietal block Ischemia)	
		11 mo	0 08	60	Pos	30	Lat	40	Normal	
30	11	4 days	0 08	−50	Ant	60	Pos	100	Parietal block	Death
		5 days	0 08	−30	Ant	60	Pos	100	Parietal block	
31	10	6 days	0 06	0	Lat	60	Lat.	60	Parietal block	Death
		7 days	0 09	0	Pos	60	Lat	120	Parietal block	
32	5	16 days	0 08	−30	Pos	60	Ant	150	Parietal block	Death
		46 day	0 07	30	Pos	0	Pos	40	Normal	
33	3	5 days	0 07	30	Lat	60	Pos	45	Prolonged Q T	Death
		10 days	0 09	−30	Pos	100	Lat	130	Parietal block	
		19 day	0 07	−30	Pos	30	Pos	60	Parietal block	
		41 days	0 07	30	Pos	30	Lat	30	Normal	

*Intraventricular conduction block was the most severe ECG abnormality of patients in Group C. Parietal block is defined in the text.

respiratory failure that complicated polyneuritis Case 32 was a 5 year old child whose death was due to polyneuritis and respiratory failure but in whom the block had disappeared by the forty sixth day of illness In only 1 surviving patient (Case 29) had the parietal block disappeared at follow up examination 11 months after the onset of diphtheria The block had persisted in the other 3 survivors (Cases 25 26 and 28) for 4 months 22 days and 11 months respectively

D Major conduction block This group comprised 14 patients with either complete bundle branch block or complete A V block Only 3 survived The mean greatest width of QRS was 0 125 second The QRS T angle was widened in all but receded to within the limit of normal in 5 patients of these 2 died Significant features of the electrocardiograms appear in Table V

Complete right bundle branch block appeared in 2 children one recovered (Case 34) after having developed the block on the tenth day of illness with return to normal on the twenty second day The other died (Case 35 Table VI) this child had parietal block involving the left ventricle on the fifth day and complete right bundle branch block on the eighth day associated with low sodium syndrome

The electrocardiograms of 4 children revealed complete left bundle branch block

*Table V Major conduction block**

Case	Age (yr)	Time of ECG after onset	QRS duration (sec)	QRS axis		T axis		QRS T spatial angle (degrees)	ECG diagnosis	Remarks
				Frontal (degrees)	Horizontal	Frontal (degrees)	Horizontal			
34	6	10 days	0 12	120	Lat	60	Pos	130	Right BBB	Recovery
								QRS–ST=180		
		11 days	0 12	120	Lat	60	Pos	130	Right BBB	
								QRS–ST=180	Nodal rhythm	
		15 days	0 07	60	Lat.	60	Ant	20	Ischemia	
								QRS–ST=180		
		22 days	0 07	30	Lat	30	Lat	0	Prolonged P R	
		22 days	0 07	45	Pos	45	Pos	0	Normal	
35	8	4 days	0 07	45	Pos	60	Lat	30	Prolonged Q-T	Death
		5 days	0 08	−60	Pos	60	Ant	150	Parietal block	
		8 days	0 14	−160	Ant	30	Ant	180	Nodal rhythm Right BBB	
36	5	6 days	0 06	75	Pos	−120	Pos	180	Ischemia	Recovery
		12 days	0 12	−30	Pos	120	Ant	180	Left BBB Prolonged P R	
		6 wk	0 08	60	Pos	30	Lat	60	Normal	
37	11	6 days	0 06	15	Lat	15	Pos	60	Normal	Recovery
		23 days	0 12	30	Pos	60	Ant	130	Left BBB	
		25 days	0 08	60	Pos	60	Pos	45	Normal	
		4 yr	0 08	30	Pos	60	Pos	45	Normal	
38	4	11 days	0 06	30	Pos	−30	Pos	75	Ischemia	Death
		20 days	0 11	0	Pos	−150	Ant	150	Left BBB	
		31 days	0 07	60	Pos	0	Lat	75	Ischemia	
39	9	6 days	0 08	60	Pos	30	Lat	0	Normal	Death
		12 days	0 09	100	Pos	−60	Ant	150	Ischemia	
		25 days	0 12	−30	Pos	−30	Ant	160	Left BBB	
		41 days	0 09	60	Pos	−90	Ant.	160	Ischemia	
40	4	11 days	0 16	120	Ant	−60	Pos	180	Complete A V block	Death
41	2½	4 day	0 11	−60	Lat	90	Inf	150	Complete A V block	Death
		5 days	0 16	−80	Sup	120	Lat	180	Complete A V block	
4	7	7 day	0 08	90	Inf	60	Pos	60	Prolonged Q-T	Death
		10 day	0 13	−40	Pos	120	Ant	180	Complete A V block	
43	5	5 day	0 07	60	Pos	60	Lat	20	Ischemia	Death
								QRS–ST=180		
		7 days	0 12	−45	Pos.	120	Lat	180	Complete A V block	
44	8	7 day	0 12	60	Pos	−150	Ant	160	Complete A V block	Death
45	8	10 days	0 12	0	Pos	100	Ant	150	Complete A V block	Death
46	2	6 day	0 09	−130	Ant	120	Pos	120	Complete A V block	Death
		11 day	0 07	75	Pos	−90	Pos	165	Ischemia	
		27 days	0 07	100	Pos	30	Pos	0	Ischemia	
47	5	7 day	0 11	120	Ant	−60	Pos	180	Complete A V block	Death

[illegible] Group D had ECG evidence of compl[illegible] right or left b[illegible] branch block or compl[illegible] A V block.

Table VI. Clinical and pathologic summary of autopsy cases

Case	*Age (yr.)*	*Day of illness*	*Clinical diagnoses*	*ECG diagnosis*
31	10	6	Obstructive tracheobronchial diphtheria, distant, muffled heart sounds	Parietal block
		8	Cyanosis, suffocation, serum K 5.3, CO_2 35 mEq./L., pCO_2 84 mm. Hg, pH 7.17, respiratory acidosis	
33	3	5	Nasopharyngeal diphtheria	Q-T prolonged
		8	Heart sounds distant	
		12	Premature ventricular beats, diastolic gallop, systolic murmur	Parietal block
		36	Low Na^+ syndrome, polyneuritis, Na^+ 115, Cl 96, CO_2 18 mEq./L. Heart sounds normal	
		41	Respiratory failure	Normal
35	8	4	"Bull neck" diphtheria	Q-T prolonged
		5	Tracheotomy	Parietal block
		8	Heart sounds distant, low Na^+ syndrome, serum Na^+ 117, K 4.9, Cl 79, CO_2 20 mEq./L.	Right BBB
		9	Pulmonary congestion, probable left heart failure	
38	4	11	Nasopharyngeal diphtheria	Mild ischemia
		20	Congestive heart failure	Left BBB
		26	Heart compensated	
		31	Polyneuritis, heart sounds normal	Mild ischemia
		34	Respiratory failure	
40	4	11	"Bull neck" diphtheria, congestive heart failure, shock	Complete A-V block
44	8	4	"Bull neck" diphtheria, heart sounds normal	
		7	Congestive heart failure	Complete A-V block
		10	Shock	
46	2	4	Nasopharyngeal diphtheria, hypersensitivity reaction to diphtheria antitoxin	
		6		Complete A-V block
		11-24	Premature ventricular beats	Ischemia
		27	Polyneuritis	Mild ischemia
		30	Respiratory failure	
47	5	7	Nasopharyngeal diphtheria, congestive heart failure	Complete A-V block
		8	Shock	

at a mean time of 20 days after the onset of illness. The block subsided in all. The tracings returned to normal in 2 patients who recovered (Cases 36 and 37). Those who died, Cases 38 and 39, revealed the block on the twentieth and twenty-fifth days, respectively, preceded by ECG diagnoses of ischemia and in association with congestive heart failure. Case 38 (Table VI) afforded an example of the most severe clinical involvement of the myocardium with corresponding regression of clinical

Pathologic diagnoses	*Heart*	
	Gross	*Microscopic*
Tracheo-bronchial diphtheria with membrane obstructing airway Myocarditis Nephrosis	220 Gm flabby dilated	Interstitial edema striations well retained
Necrotizing bronchopneumonia secondary to aspiration of food Congestion of liver and spleen Focal myocarditis mild	110 Gm flabby dilated	Interstitial edema mild fibrinoid degeneration occasional focal round cell infiltration
Interstitial pneumonia Pulmonary edema Nephrosis Myocarditis mild	125 Gm dilated petechiae hemorrhages	Numerous small hemorrhages scattered areas of inflammatory cells
Pulmonary edema Congestion of liver and kidney Myocarditis	120 Gm dilated congested	Scattered focal areas of inflammatory cells few Anitschkow cell mild edema
Myocarditis severe Pulmonary edema Congestion of liver	110 Gm dilated pale	Exten necrosis of muscle cells infiltration of plasma cell and lymphocytes
Myocarditis Pulmonary edema	136 Gm flabby dilated	Fibrinoid degeneration focal infiltrate of monocytes and lymphocytes tiny hemorrhages
Necrotizing tracheobronchitis due to aspiration of food Pulmonary edema Degeneration and edema of brain and spinal cord Congestion of liver kidney spleen	65 Gm dilated	Few rare and widely scattered areas of perivascular cuffing with lymphocytes
Tracheobronchitis due to aspiration of food Pulmonary edema and hemorrhage Toxic nephrosis Myocarditis	93 Gm dilated firm pale mottled	Proliferation of reticulocytes interstitial edema hyaline degeneration occasional polymorphonuclear nd mononuclear cell infiltration

and ECG signs prior to death from polyneuritis and respiratory failure and with histologic evidence of the myocardium undergoing reparation Case 39 failed to respond adequately to measures for congestive failure the conduction block subsided but the QRS T angle remained wide until the time of death at 41 days

The other 8 patients in this group (Cases 40 47) had arrhythmias in the form of complete A V block heralding a fatal outcome for all Autopsy of 3 patie

(Cases 40 44 and 47 Table VI) who died on the eleventh tenth and seventh days respectively after the onset of nasopharyngeal bull neck diphtheria and who terminally exhibited signs of congestive heart failure and circulatory collapse revealed the most severe histologic evidence of myocarditis (Table VI) Four others (Cases 41 42 43 and 45) had this same malignant nasopharyngeal type of illness and died with signs of shock The eighth patient (Case 46 Table VI) revealed contrasting effects of diphtheria on the ECG and on the cellular structure of the myocardium as observed at autopsy Complete A V block had subsided by the eleventh day Thereafter frequent premature ventricular beats and ECG evidence of ischemia coincided through the twenty seventh day when the QRS T angle became nearly normal Death resulted from polyneuritis and respiratory failure on the thirtieth day The myocardium appeared to be normal except for a few widely scattered capillaries with peripheral accumulation of lymphocytes which according to the pathologist were not extensive enough to dignify the diagnosis of myocarditis This case represented the only example of complete A V block without widening of QRS by at least 0 03 second

Comment

The organs affected in diphtheria are primarily those with high energy requirements cardiovascular organs peripheral nerves endocrine glands mucous membranes and renal tubular epithelium It is not surprising therefore that all children with fatal diphtheria in our group had clinical and electrocardiographic evidence of myocardial involvement Anderson[20] also found similar evidences of myocarditis in all of 13 fatalities due to diphtheria in his series The progression and regression of positive physical findings and ECG abnormalities allude to the limitations in correlating these signs with autopsy data

Many manifestations of diphtheria are consistent with the view that it is basically a disturbance of cellular respiration Pappenheimer[1] and Pappenheimer and Hendee demonstrated the diphtheria toxin to be the protein moiety of cytochrome b an enzyme functioning as an electron acceptor in aerobic respiration of *Corynebacterium diphtheriae* The mode of action of the toxin is apparently that of a competitive analogue in cellular respiration in man the only natural host of the organism There are widespread effects on functions of the cells and tissues but only after a delay during which time the host s cytochrome b becomes depleted The electrons then accumulate along the respiratory chain and the redox systems in the cells remain reduced Oxidation cannot occur and energy as the high energy phosphate bond in the synthesis of ATP is not released The degree of suffocation determines the extent of cellular necrosis and its sequelae

The effects of diphtheria upon the myocardium appear to be manifested in ECG abnormalities in two phases The first may appear as delayed or completely blocked A V conduction proportionate to the clinical severity of the disease The second phase is probably due to the initial onslaught or a progression of metabolic or biochemical changes within the myocardium which may result in loss of conductivity through Purkinje tissue There may be left axis deviation due to parietal block and then widening of QRS as the ECG simulates complete bundle branch block The pathogenesis of these ECG anomalies is discussed in more detail below

Scher[3] indicated that the small cells which lie between the atrial fibers and the upper region of the A V node have the lowest safety factor and are most susceptible to depression by anoxia or other factors A V conduction blocks both incomplete and complete occur here rather than in the larger nodal cells The occurrence of the A V blocks at similar times in our Groups A (prolonged P R) and D (major conduction block) is compatible with the view that a similar type of injury was involved in these cases representing clinically both the mildest and the severest examples of diphtheria More extensive myocardial affection of cases in Group D is discussed below First degree A V block persisted in the majority of cases similar to the findings of Hoel and Berg[11] who

noted this delay in A-V conduction for over 5 years after the onset of diphtheria. Complete A-V block most commonly terminates in death, although Engle's cases[4] furnish a prominent exception.

Affection of the ventricles was commonly manifested only as a metabolic disturbance (Group B) that involved repolarization of the membrane of myocardial cells and without widening of QRS. Brooks and associates[3] found the time course of repolarization in the transmembrane action potential to be in direct relation to the amplitude and direction of T waves in the focal unipolar electrogram. T waves in our cases became low in amplitude and then changed direction, causing the QRS-T angle to widen. Only when the latter event occurred were the changes presumed to be due to the effect of the diphtheria toxin. It is probable that some cases with significant diphtheritic involvement of the myocardium were not recognized by this criterion. Physical signs of carditis may be of short duration and therefore undetected, and the ECG may reveal only depression of T wave amplitude without widening of the QRS-T angle. Conversely, T wave inversion may have resulted from electrolyte imbalance and acidosis secondary to pathology involving mainly other organ systems and is not of itself evidence of myocardial disease. Without doubt the effects of renal tubular and respiratory disease contributed in some cases to T wave changes, probably those appearing in the later stages of the disease.

A conduction block involving the anterior superior division of the left main bundle branch to the left ventricle was termed "parietal block," as described by Grant.[11] The term was applied to all cases of Group C except one, a child with incomplete right bundle branch block that persisted only to the eleventh day of illness. Since there is free anastomosing of Purkinje fibers between the anterior and posterior divisions of the left bundle branch, there was little delay in ventricular excitation, but the terminal forces through the left ventricle were directed superiorly and leftward. This resulted in left axis deviation of QRS and widening of the QRS-T angle. The death of 4 of 8 patients who showed this sign as the most severe ECG abnormality is evidence of its importance in diphtheria. In animal studies, Alzamora-Castro and associates[6] induced "parietal" or "focal" block by injections of cocaine into branches of coronary arteries and designated the ECG anomaly "fiber block" to indicate a disturbance of the contractile muscle elements. Although a conduction block may be induced in this manner, such an ECG anomaly is compatible with normal ventricular muscle.

It seems probable that such a fiber block as mentioned above contributed to prolongation of ventricular depolarization in all 11 patients of Group D. Widening of QRS complexes was of abrupt onset rather than gradual, similar to the findings of Grant and Dodge[17] in other types of acquired heart disease. Their data indicated that in one third of the cases which simulated left bundle branch block, the disturbance that caused the delayed conduction was within the left ventricle distal to the main branch of the left bundle. In diphtheria, the diffuse biochemical changes secondary to anoxia caused loss of conductivity through the Purkinje network and resulted in intramyocardial spread of the impulse as a wave front. The ECG vectors plotted from the maximal deflections of T (repolarization) were opposite in direction to those vectors of QRS (depolarization). When the myocardium had recovered sufficiently, the Purkinje tissue regained its function, with abrupt shortening of QRS complexes. This sequence of events was observed best in Cases 36-39 with left bundle branch block, three of which revealed evidence of ischemia prior to the onset of delayed conduction. Although the widening of QRS regressed in all 4 cases, the QRS-T angle returned to normal in only 2, which evidence suggests a severe metabolic disturbance of the myocardium in these patients with bundle branch block. This finding indicates that the difference between primary and secondary T wave changes in our cases was mainly one that was related to the severity of the disease.

Our data are consistent with a view that the ECG affords a sensitive index of the histotoxic effect of diphtheria on the myocardium. When ECG changes show consistent evidence of regression, the myo

cardium is undergoing improvement Pathologic changes in the myocardium may not be apparent in subsequent histologic studies After signs of carditis regress the clinician may safely dispense with measures which may have been necessary for managing congestive heart failure but which may have adverse effects on a patient expected to have adrenal cortical disease and possibly a deficiency of the salt retaining hormone Only one late occurring death could be attributed to congestive heart failure or circulatory collapse The process of recovery of the myocardium may be coincident with progressive neural degenerative changes which in our series was responsible for late occurring death in 4 patients These latter patients have a tendency to aspirate nasopharyngeal secretions but may also be expected to recover if adequate pulmonary ventilation and hormonal balance can be maintained and if secondary infection can be controlled

Summary

Hospital records of 229 children with diphtheria revealed evidence of myocarditis affecting 47 (20 per cent) both by physical signs and abnormal electrocardiograms The 437 electrocardiograms taken on the 47 patients were analyzed by the conventional and the electrovectorcardiographic method of Grant and the QRS T spatial angles were evaluated A high predictability of survival from diphtheria is afforded by the electrocardiogram

Cases were grouped according to their most severe ECG abnormalities If only the P R interval was prolonged (Group A) or the T vector was shifted (Group B) causing the QRS T angle to widen the prognosis for complete recovery was excellent Prolongation of the P R interval tended to persist whereas primary T wave changes subsided An intraventricular block (Group C) involved the superior branch of the left main bundle branch to the left ventricle in 8 children and of these 4 died but only one as a result of myocarditis One child with only incomplete right bundle branch block recovered Of 14 children with a major conduction block (Group D) 11 died Six of these children had complete bundle branch block there were 3 fatalities Complete A V block was the most ominous ECG sign in that it was consistently followed by death in 8 children However in one of these children the block regressed and death resulted from polyneuritis and respiratory failure

Out of the total 229 cases 15 deaths occurred in that group of 47 patients in whom there was evidence of myocardial involvement 10 deaths were due to this involvement and peripheral vasodilatation One child died early from obstructive laryngeal diphtheria and 4 succumbed to the late effects of progressive polyneuritis complicated by pulmonary hypoventilation and infection

Autopsy was carried out on 8 children for whom correlations of ECG clinical and pathologic data were presented Early death in 3 children (Cases 40 44 and 47) was associated with complete A V block and histologic evidence of extensive myocardial disease and in one child (Case 35) with right bundle branch block and a hemorrhagic myocardium The child who died early from laryngeal obstruction (Case 31) had parietal block by ECG and interstitial edema of the myocardium Death due to peripheral neural and respiratory causes late in the course of illness of 3 children (Cases 33 38 and 46) was associated with regression of ECG changes and much less severe histologic evidence of myocarditis

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Dilatation of the pulmonary trunk in stenosis of the pulmonary valve and of the pulmonary arteries in children

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Dilatation of the pulmonary trunk in pulmonary valvular stenosis has been a subject for comment and speculation with regard to its pathogenesis for more than a century.[1-6] However, the literature contains only vague generalizations about the relationship of the degree of post-stenotic dilatation to the severity of the valvular stenosis and the frequency of its incidence in childhood. Careful quantitative studies of dilatation of the pulmonary artery in this condition have been very few. Van Buchem's series[7] consisted exclusively of adults. The excellent study of Rudhe and associates[8] included only 4 patients under 3 years of age.

The aim of the present study was to determine whether any direct relationship exists between the degree of poststenotic dilatation of the pulmonary trunk and age, severity of stenosis, or presence of additional shunting defects which increase pulmonary blood flow. A similar correlative study of the size of the pulmonary trunk in isolated bilateral stenosis of the pulmonary arteries was also made.

Our findings revealed that there is no conclusive correlation between poststenotic dilatation of the pulmonary trunk and the severity of the stenosis or age of the patient. Contrary to prevalent notions that dilatation of the pulmonary trunk is rare in very early childhood, we found that it is quite common during infancy.

Material and methods

The hemodynamic and angiocardiographic data on 88 patients with pulmonary valvular stenosis and 15 patients with isolated bilateral pulmonary artery stenosis were reviewed. For the purpose of this study, the cases were divided into

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the following categories isolated pulmonary valvular stenosis 65 cases pulmonary valvular stenosis + left to right shunt 7 cases pulmonary valvular stenosis + stenotic lesions of the pulmonary arteries 13 cases pulmonary valvular stenosis + left to right shunt + stenotic lesions of the pulmonary arteries 3 cases isolated bilateral pulmonary artery stenosis 15 cases

Among 7 patients with left to right shunts the shunting defect consisted of a ventricular septal defect in 3 and an atrial septal defect in 4 The ages of the patients in the entire series varied from 1 month to 19 years There were 41 patients below 1 year of age 30 patients between 1 and 4 years 26 patients between 4 and 12 years and 6 patients over 12 years of age

Selective angiocardiography with injection of contrast material into the right ventricle was performed in approximately three fourths of the patients In the remainder the contrast substance was injected into either the right atrium or a peripheral vein The angiocardiograms were obtained simultaneously in the anteroposterior and lateral projections using the Elema Schonander roll film serial changer at a frequency of 8 exposures per second for the first second and 4 per second for the succeeding 5 to 8 seconds

The dextroangiocardiograms in the lateral projection and the levoangiocardiograms in the same projection were analyzed The exposures obtained during ventricular systole were selected and from these the maximal diameter of the pulmonary trunk and that of the ascending aorta were measured in each case The maximum diameter of the pulmonary trunk was usually found at the level of its middle third or at the junction of the middle and distal third The *maximum* diameter of the aorta was measured at the vertical part of the ascending aorta since this segment usually has a uniform caliber No measurements were made at the level of the aortic sinuses of Valsalva or immediately above them where a slight relative constriction is often normally present

The ratio of the diameter of the pulmonary trunk to that of the aorta was then calculated and was used to express the relative size of the pulmonary trunk To provide a base line for comparative purposes the lateral angiocardiograms of 30 other children who were 3 days to 17 years of age and who had normal cardiovascular systems were similarly analyzed and the ratio of the pulmonary trunk to aortic diameter was plotted against age (Fig 1)

The validity of using this ratio in the present study as an expression of the relative size of the pulmonary trunk is of course based on the assumption that the aortic caliber was normal Thus it would not be reliable if lesions that cause dilatation of the ascending aorta such as Marfan's syndrome or aortic stenosis were present No such associated conditions existed in any of our patients

Catheterization of the right side of the heart was performed in all patients This was done either on the same day as the angiocardiographic procedure or within a few weeks of it The pulmonary trunk was not entered in 11 patients and for this reason the severity of the pulmonary obstruction was expressed by the level of the peak right ventricular systolic pressure

In order to equate the degree of dilatation of the pulmonary trunk with the functional severity of the pulmonary stenosis the ratio of pulmonary trunk to aortic diameter was plotted against the right ventricular systolic pressure of the patients with isolated and with complicated pulmonary valvular stenosis (Fig 2) The influence of age upon the poststenotic dilatation was also evaluated by plotting the same parameter against age (Fig 3) Similarly the size of the pulmonary trunk in the patients with isolated bilateral stenosis of the pulmonary arteries was plotted against the peak right ventricular systolic pressure and against age (Fig 4)



Fig 1 The pulmonary trunk/aortic ratio plotted against age in series of 30 normal subjects

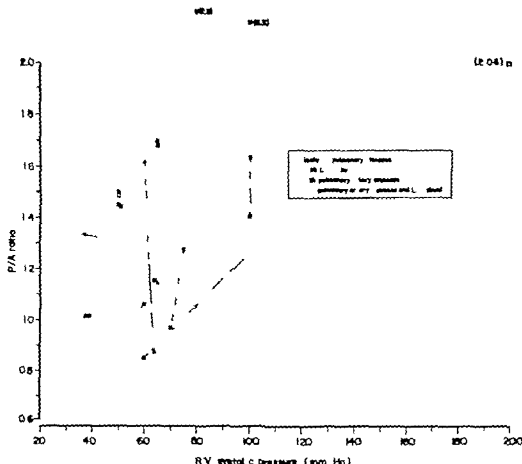


Fig 2 Pulmonary trunk/aortic ratio plotted against peak right ventricular systolic pressure in 88 cases of pulmonary valvular stenosis (The arrows represent the 7 patients on whom serial studies were made)

Results

The mean pulmonary trunk/aortic ratio in the 30 children with a normal cardiovascular system was 1 06 (± 0 044) which indicates that under normal circumstances the diameter of the pulmonary trunk is usually slightly bigger than or the same size as that of the aorta (Fig 1) A similar finding was observed by De la Cruz and associates[4] in their study of normal autopsy material in children

Only one patient in this normal series had a pulmonary trunk/aortic ratio of more than 1 2 and only one had a ratio of less than 0 9 From this data we assumed that a pulmonary trunk/aortic ratio of more than 1 2 suggests dilatation of the pulmonary trunk and that a ratio of less than 0 9 suggests *narrowing of the* pulmonary trunk presuming of course *that aortic size is normal*

In Fig 2 the relationship between pulmonary trunk/aortic ratio and peak right ventricular systolic pressure is shown It is obvious in this graph that there was no apparent correlation between the severity of pulmonary stenosis and the degree of poststenotic dilatation of the pulmonary trunk However *of the 10 patients* who had right ventricular pressures greater than 110 mm Hg 4 had pulmonary trunk/aortic ratios of 1 75 or greater whereas of the 78 patients with right ventricular pressures below 110 mm Hg only 9 had pulmonary trunk/aortic ratios of 1 75 or greater Although this may suggest that severe dilatation of the pulmonary trunk occurs more often in severe pulmonary stenosis there are not enough patients at the upper end of the right ventricular pressure scale to allow one to draw a definite conclusion Of the 65 pa

tients with isolated pulmonary valvular stenosis there were 15 (23 per cent) with a pulmonary trunk/aortic ratio of 1 2 or less hence without definite dilatation of the pulmonary trunk Five of the 13 patients with combined pulmonary valvular and pulmonary arterial stenosis and all 3 patients with the same combined lesions plus an accompanying left to right shunt also did not reveal definite enlargement of the pulmonary trunk In fact 3 patients with associated pulmonary artery stenosis revealed pulmonary trunk/aortic ratios of less than 0 9 On the other hand all 7 patients with combined pulmonary valvular stenosis and a left to right shunt had prominent poststenotic dilatation of the pulmonary trunk

Poststenotic dilatation of the pulmonary trunk was present in 16 of 24 patients (67 per cent) with isolated pulmonary stenosis who were studied during the first

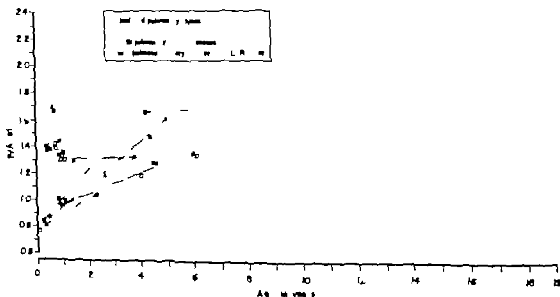


Fig 3 Pulmonary trunk/aorta ratio plotted against age in 88 cases of pulmonary valvular stenosis (The arrows represent the 7 patients on whom serial studies were made)

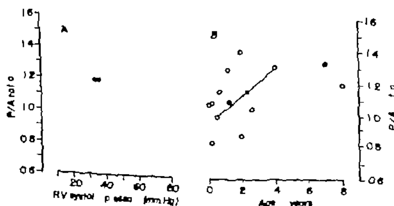


Fig 4 The pulmonary trunk/aortic ratio plotted against peak right ventricular systolic pressure and against age in 15 cases of bilateral pulmonary artery stenosis One patient for whom there were two serial angiocardiograms is represented by the arrow

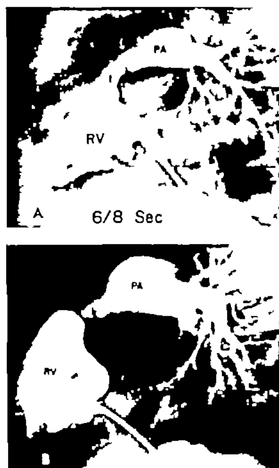


Fig 5 Serial angiocardiogram in a patient with isolated pulmonary valvular stenosis obtained at 3 months (*A*) and 2 years (*B*) of age showing progression of the poststenotic dilatation An unusual feature of this case is the very narrow pulmonary annulus with poststenotic dilatation affecting only the distal pulmonary trunk The arrow indicates the jet emerging from the stenosed valve *RV* Right ventricle *I* Infundibulum *PA* Pulmonary artery

year of life in 34 of 46 patients (74 per cent) under the age of 4 years and in 16 of 19 patients (84 per cent) over 4 years of age (Fig 3) Thus there was a slightly higher incidence of poststenotic dilatation in the older age group Of the 6 patents with isolated pulmonary valvular stenosis and 1 patient with pulmonary valvular stenosis associated with an atrial septal defect who underwent angiocardiography a second time after an interval of from 1 to 5 years 5 showed a significant increase in dilatation of the pulmonary trunk and 2 did not

The degree of obstruction to pulmonary blood flow in 15 patients with isolated bilateral pulmonary artery stenosis varied from mild to moderate the peak right ventricular systolic pressure varied from the upper normal range to 70 mm Hg In these 15 patients the pulmonary trunk/aortic ratio was within the normal range in 11 and over 1 2 in 4 (Fig 4) Because of the small number of patients it is not possible for one to draw any definite conclusion in regard to the relationship of the size of the pulmonary trunk to either the age of the patient or the severity of the stenosis A comparison of Fig 2 with Fig 4 readily shows that dilatation of the pulmonary trunk was more marked in the patients with pulmonary valvular stenosis than in those with bilateral pulmonary artery stenosis

Discussion

There are a number of theories pertaining to the pathogenesis of poststenotic dilatation of the pulmonary trunk It has been attributed to congenital weakness of the arterial wall[9] endarteritis[10] and tuberculosis[11] among other things An explanation based on purely physical factors seems most likely and has experimental support[1, 14] However the precise nature of the mechanical factors which affect the arterial wall and lead to the production of dilatation is uncertain A direct local effect on the arterial wall by the jet of blood ejected through the stenotic orifice is unlikely since the dilatation of the pulmonary trunk is usually generalized

Holman[1] mentioned two basic factors (a) transformation of the kinetic energy of the blood passing with high velocity through the stenotic valve to high lateral pressure exerted on the vessel wall beyond the stenosis and (b) structural fatigue of the vessel wall which is directly related somehow to turbulence of flow Roach[14] has recently presented excellent experimental work on poststenotic dilatation of systemic arteries which demonstrates the relationship of turbulence of flow to weakening of the vessel wall Bruns and associates[15] attribute poststenotic dilatation to vibration of the vessel wall due to periodic fluctuations in the blood downstream from

the constriction. Hugh and Fox[18] have recently rekindled interest in the theory that cavitation in the blood stream distal to the stenosis is the chief mechanism responsible.

Holman produced poststenotic dilatation in rubber tubes in a matter of 21 to 90 hours by allowing a mechanically pulsatile flow through a stenotic segment.[3] He stated that poststenotic dilatation was

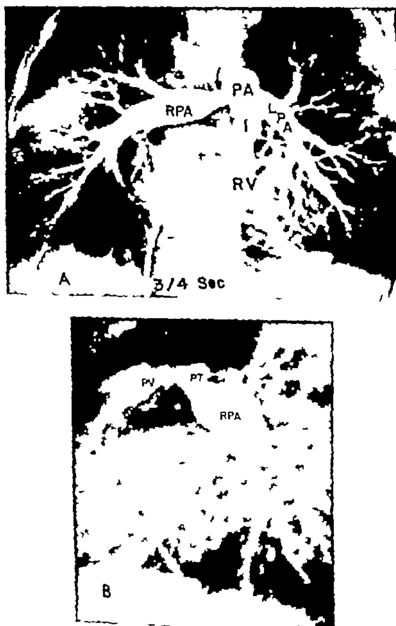


Fig. 4. Angiocardiogram (posteroanterior and lateral projections, two separate injections) of a 3½-year-old girl with both pulmonary valvular stenosis and bilateral pulmonary artery stenoses. Peak systolic pressure in the right ventricle was 125 mm Hg and in the pulmonary trunk 40 mm Hg. Note the diminutive pulmonary trunk (PT/Ao ratio 0.85). The right and left main pulmonary arteries show poststenotic dilatation. *RV*, Right ventricle; *I*, Infundibulum; *PV*, Pulmonary valve; *PT*, Pulmonary trunk; *RPA*, Right pulmonary artery; *LPA*, Left pulmonary artery.





Fig 7 Two patients who illustrate anatomic variations in the configuration of the pulmonary trunk in isolated pulmonary valvular stenosis 1 Patient A C J 9 months old RV (systolic) 76 mm Hg B Patient B V B 19 years old RV, (systolic) 8 mm Hg

found in dogs 24 to 84 days after experimental stenosis of the thoracic aorta Rodbard and associates[16] produced poststenotic dilatation of the aortic arch in chicks within 4 weeks These studies suggest that poststenotic dilatation of a blood vessel may develop within a relatively short period of time On the other hand there is a prevalent notion that dilatation of the pulmonary trunk in cases of pulmonary valvular stenosis is rare in infancy and early childhood Kjellberg[17] stated that it is uncommon in children under 4 years of age although it is the rule thereafter Rudhe and associates[4] noted its absence in only 4 of 39 patients with pulmonary valvular stenosis 2 of these 4 patients who had no poststenotic dilatation were 2 years of age However only 4 of Rudhe s entire series were under 3 years of age It is evident from our data that poststenotic dilatation of the pulmonary trunk appears as early as during infancy This seems to be compatible with the experimental studies of Holman and Rodbard and co workers

It is not known whether dilatation of the pulmonary trunk is already present during intrauterine life It is likely that the great increase in pulmonary blood flow immediately after birth is an important factor in accelerating its development Our studies suggest that the amount of blood flowing through the stenosed valve has some influence on the severity of the poststenotic dilatation Thus all 6 patients who had pulmonary valvular stenosis associated with left to right shunts in this series had gross dilatation of the pulmonary trunk some of the highest ratios of the diameter of the pulmonary trunk to that of the aorta were found in this group We do not yet have data which bear on the relationship of the pulmonary trunk/aortic ratio to pulmonary blood flow in the absence of stenosis

It was not the purpose of this paper to study the mechanism of production of poststenotic dilatation of the pulmonary trunk nor did our investigation include a survey of all possible factors that might account for the enlargement of the pulmonary trunk in this condition Our data merely demonstrated that the severity of pulmonary valvular stenosis and age of the

patient did not appear to have an important bearing on the degree of poststenotic dilatation (Fig 5) Since our oldest patient was 19 years old we have no data pertaining to the natural history of poststenotic dilatation of the pulmonary trunk in adult life In 5 of the 7 patients who were subjected to serial angiocardiographic studies apparent progression of the dilatation of the pulmonary trunk was observed It is worth while to emphasize that although our data suggest that age had but a slight influence on the poststenotic enlargement of the pulmonary artery in a group of patients with isolated pulmonary stenosis time may have some influence on the progression of the dilatation of the pulmonary trunk in individual patients For such a conclusion to be made serial angiocardiographic studies on a large number of patients is necessary

The interrelationship between pulmonary valvular stenosis pulmonary artery stenosis and poststenotic dilatation is very interesting but has received scarcely any attention in the literature hitherto The association between pulmonary valvular stenosis and stenotic lesions of the pulmonary arteries was commented on by Moncl eberg [19] and has been encountered in recently reported series[1, 20] (Fig 6) Stenotic lesions of the pulmonary artery branches may or may not be accompanied by dilatation of the arterial segments immediately distal to the stenotic areas If the stenosis is of the diffuse hypoplastic type the entire pulmonary arterial tree is narrow and spidery without dilatation of any segment of it More often however angiocardiography reveals localized stenotic segments with dilatation of variable length and degree existing distal to the stenosis The stenotic areas occur either at the bifurcation of the pulmonary trunk or in multiple secondary or tertiary branches usually at their points of origin Dilatation of the pulmonary trunk in patients with isolated bilateral pulmonary artery stenosis is of mild degree if present at all This dilatation of the pulmonary trunk constitutes prestenotic dilatation and must be related to its hemodynamic role as a small compression chamber The frequent absence of this prestenotic dilatation may be related to some inherent structural abnormality of the pulmonary artery wall which prevented its physiologic expansion after birth In the presence of combined pulmonary valvular and pulmonary artery stenosis dilatation of the pulmonary trunk appears to be significantly less marked than in those with isolated pulmonary valvular stenosis One possible explanation may be that some intrinsic abnormality of the vessel wall in these cases resists the physical forces responsible for the dilatation Another possibility is that the mechanics of flow and of turbulence in the pulmonary trunk distal to the stenotic valve may be modified by the reduced size of the pulmonary artery compression chamber as a result of the bilateral narrowing of both main pulmonary arteries at their origins If the second hypothesis is correct relatively larger pulmonary trunks may be observed in cases of combined pulmonary valvular stenosis and multiple bilateral but distal peripheral pulmonary artery stenoses where the pulmonary artery compression chamber is relatively larger

Summary

The presence and degree of dilatation of the pulmonary trunk in 88 children with pulmonary valvular stenosis and in 15 children with bilateral stenosis of the pulmonary arteries was studied angiocardiographically No obvious correlation was found between poststenotic dilatation and right ventricular pressure in patients with mild to moderate severity of the valvular stenosis However 4 out of 10 patients with severe stenosis had very marked dilatation of the pulmonary trunk Our data appear to suggest that there is only a slightly higher incidence of poststenotic dilatation in older children than in infants Nevertheless the passage of time may play an important role in individual patients thus serial angiocardiograms obtained in 7 patients demonstrated some progression of the poststenotic dilatation in 5 Enlargement of the pulmonary trunk appeared to be enhanced by the presence of a left to right shunt and appeared to be partly restricted by associated stenosis of the pulmonary arteries

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Comparative effectiveness of pargyline as an antihypertensive agent

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During the past 4 years three potent hypotensive agents have been added to the antihypertensive drug armamentarium. Guanethidine, a compound which depletes the postganglionic sympathetic nerve fibers of their catecholamine stores, was introduced in 1960. Subsequently, methyl dopa, a decarboxylase inhibitor, has become available for clinical use, and pargyline, a monoamine-oxidase inhibitor, is the most recent therapeutic addition. It is the purpose of this report to comment on the use of pargyline alone and in combination with hydrochlorothiazide as an antihypertensive agent, and to compare its clinical efficacy with that of guanethidine and methyl dopa.

Methods and material

Thirty-three ambulatory patients with blood pressures greater than 150/100 mm. Hg were randomly selected from the Hypertension Clinic. Twenty-eight of the subjects were Negro and 5 were white; their ages ranged from 28 to 68 years. In each case, essential hypertension was the underlying disorder. All patients were placed initially on oral placebo medication for a minimum period of 4 weeks. The patients returned to the clinic at weekly intervals at which time blood pressure and physical signs and symptoms were recorded. After the control period, pargyline was begun in an initial oral dosage of 25 mg. daily; thereafter the dosage was increased at biweekly intervals to a maximum of 150 mg. daily (50 mg. three times a day), unless normotension (140/90 mm. Hg or less) was achieved at a lower dosage or the occurrence of side reactions prohibited the use of maximum drug dosage. Treatment with pargyline alone was continued for periods ranging from 8 to 30 weeks.

Hydrochlorothiazide was added to the therapeutic regimen in 11 patients in whom normotension was not achieved with pargyline alone. The initial dose of hydrochlorothiazide was 50 mg. per day (25 mg. twice a day); the maximum was 100 mg. daily (50 mg. twice a day). The combination of pargyline and hydrochlorothiazide was administered for periods ranging from 6 to 30 weeks.

Results

The effect of oral pargyline on blood pressure is tabulated in Table I. Of the

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Table I Response of blood pressure to pargyline alone and in combination with hydrochlorothiazide

	Number of patients	Supine				Erect			
		Normotensive		Mean blood pressure reduced > 20 mm Hg or normotensive		Normotensive*		Mean blood pressure reduced > 20 mm Hg or normotensive	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Pargyline	33	5	15	7	21	19	57	27	82
Pargyline plus hydrochlorothiazide	11	1	9	4	36	5	45	9	82

*Blood p[illegible] were reduced to 140/90 mm Hg or less

33 patients treated with pargyline alone 7 (21 per cent) had a significant* drop in mean arterial pressure in the supine position and 5 of the 7 became normotensive When the blood pressure was measured in the erect position 27 patients (82 per cent) obtained a significant antihypertensive response and 19 of the 27 became normotensive Of the 11 patients who received combined hydrochlorothiazide pargyline therapy 4 (36 per cent) obtained a significant reduction in blood pressure in the supine position and 1 of the 4 became normotensive When the blood pressure was measured in the erect position 9 patients (82 per cent) exhibited a significant reduction in blood pressure and 5 of the 9 became normotensive Tolerance to the drug was not evident in any of the patients

Side effects are recorded in Table II The most commonly encountered reactions were dry mouth gain in weight and insomnia Seven patients complained of impotence and/or failure of ejaculation Postural hypotension was observed occasionally but it always improved with careful drug dosage titration Significant gain in weight (from 7 to 15 pounds) occurred in 8 patients In the latter cases there were no clinical evidences of edema and the addition of hydrochlorothiazide to the therapeutic regimen did not reduce the gain in weight Increased appetite was noted by only 1 patient

Significant alterations in hemoglobin hematocrit white blood cell count urinalysis excretion of Bromsulphalein or serum sodium potassium chlorides and carbon dioxide combining power were not encountered during the course of pargyline therapy in any instance However the reduction in blood pressure was associated with a moderate elevation in blood urea nitrogen in 3 cases

Discussion

The clinical studies herein reported indicate that pargyline is a potent antihypertensive agent We have previously reported the cardiac and renal hemodynamic response to pargyline[1] as well as the clinical and pharmacodynamic effects of guanethidine and methyl dopa[2,3] Since these various studies were performed using similar methods of investigation and a similar hypertensive clinic population it is valid to compare the antihypertensive effects obtained

Pharmacology It is well established that arteriolar tonus is regulated in considerable part by the effect of tissue cathechol amines especially norepinephrine It is further acknowledged that norepinephrine is synthesized stored and subsequently released from granules located in the

*The [illegible] of a [illegible] (140/90 mm Hg [illegible]) [illegible] reduction [illegible] arterial blood pressure (diastolic pressure plus one third of the pulse pressure) of 20 mm Hg or more was c[illegible] to be significant

sympathetic postganglionic nerve terminals The pharmacodynamic studies of Maxwell and associates[4] demonstrated that guanethidine inhibits the peripheral response to electrical stimulation of sympathetic nerves however the drug produces no pharmacologic evidences of activity of the central nervous system or ganglionic blockade and the response to injected norepinephrine is not reduced It has been presumed therefore that guanethidine interferes with the release of norepinephrine from the postganglionic sympathetic nerve endings

According to Blaschko[5] the sequence of reactions leading to the biosynthesis of norepinephrine proceeds from the conversion of dihydroxyphenylalanine (dopa) to dopamine to norepinephrine (see Fig 1) In this sequence decarboxylation of dihydroxyphenylalanine is a requisite reaction From a pharmacologic standpoint interference with aromatic amino acid decarboxylation can be produced by the use of decarboxylase inhibitors Although more than 150 such compounds are now known methyl dopa is the only decarboxylase inhibitor currently available for clinical use

It has been amply demonstrated in various experimental animals that methyl dopa can reduce tissue levels of catecholamines That methyl dopa is also an effective decarboxylase inhibitor in man was clearly shown by Oates and co workers[6] they also demonstrated that methyl dopa

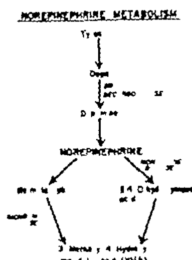


Fig 1 One of the major biopathways involved in the synthesis and degradation of norepinephrine is illustrated along with the sites of action of dopa decarboxylase and monoamine oxidase

possesses antihypertensive effectiveness in man Although it seems logical to assume that the antihypertensive response obtained with methyl dopa is related to inhibition of norepinephrine biosynthesis with resultant lowering of tissue levels of catecholamines this assumption remains unconfirmed In fact reasonable doubt exists that decarboxylase inhibition and reduction in blood pressure are related[7] Further studies are required to define the precise antihypertensive mechanism of the decarboxylase inhibitors

The enzyme monoamine oxidase (MAO) is active in the process of oxidative deamination which is one of the important biopathways for the metabolic degradation of catecholamines (see Fig 1) It is noteworthy however that alternate pathways of catecholamine metabolism also exist the most important being o methylation which involves the enzyme catechol-o methyl transferase

It is interesting although seemingly paradoxical that the reduction in blood pressure should be accomplished by agents (such as the MAO inhibitors) which cause increased tissue concentrations of catecholamines Numerous experimental studies have been conducted during recent years in an attempt to elucidate the antihypertensive mechanism (

Table II *Side effects encountered with pargyline alone*

Side effect	Number of patients	Per cent
Dry mouth	10	30
Gain in weight	8	24
Impotence or failure of ejaculation	7	46
Insomnia	6	18
Drowsiness	5	15
Anxiety	4	12
Nightmares	3	9
Blurred vision	2	6
Constipation	2	6

*Seven of 15 male patients.

mine oxidase inhibitors.[8] As yet, however, the precise mechanism responsible for a reduction in blood pressure remains undetermined.

Hemodynamic effects. The acute antihypertensive response to guanethidine is characterized by a significant reduction in cardiac output, whereas peripheral vascular resistance remains essentially unchanged.[2] The renal hemodynamic effects include a decrease in renal blood flow and glomerular filtration rate. It is notable that the effect of guanethidine upon cardiac output, renal blood flow, and glomerular filtration rate is essentially the same as that obtained with ganglion blocking agents. These hemodynamic effects demand that guanethidine, as well as the ganglioplegic drugs, be used with caution in hypertensive patients who have accompanying cardiac and vascular insufficiency. In the latter instances, guanethidine must be titrated with particular care, and the blood pressure reduced slowly.

In contrast with guanethidine, cardiac hemodynamic studies in patients with essential hypertension have demonstrated that methyl dopa lowers blood pressure mainly by reducing peripheral vascular resistance, whereas changes in cardiac output generally are minor and insignificant.[3] Although the antihypertensive effect obtained is somewhat greater in the erect position, a significant reduction in blood pressure occurs in the supine position as well. During the antihypertensive response obtained with methyl dopa, renal vascular resistance is significantly and consistently reduced; therefore, renal blood flow and glomerular filtration tend not to be compromised.

From a hemodynamic standpoint, pargyline appears to exert its antihypertensive effect by decreasing the peripheral vascular resistance, but cardiac output is not significantly altered.[1] Renal vascular resistance is reduced also, but to a lesser extent than that obtained after the administration of methyl dopa. As a result, renal blood flow and glomerular filtration rate usually decrease to a moderate extent.

Clinical application. From a clinical standpoint, it has been demonstrated that guanethidine possesses hypotensive potency similar to that of the ganglion blocking compounds.[9] The antihypertensive response obtained is most marked in the erect position; however, in contrast with the ganglioplegic drugs, guanethidine produces a reduction in blood pressure without the associated side effects due to parasympathetic blockade. Overall, the lesser incidence of side reactions, lack of parasympatholytic effects, and prolonged duration of action constitute significant clinical advantages for guanethidine in comparison with the ganglion blocking drugs. The addition of a thiazide diuretic increases the antihypertensive response in the supine position and decreases the dosage requirement of guanethidine.

Numerous clinical studies have confirmed the antihypertensive effectiveness of methyl dopa in hypertensive patients. It has been amply demonstrated also that the hypotensive effect is potentiated by the concomitant administration of diuretic agents.[3] Side reactions with methyl dopa include transient drowsiness, dry mouth, nausea, and nightmares; less common untoward effects are psychic depression, febrile reactions, and alterations in hepatic function. However, the over-all incidence of accompanying side reactions is low, and therefore the drug does appear to offer a significant contribution to the current antihypertensive drug armamentarium. Its ability to consistently reduce renal vascular resistance suggests particular usefulness for those hypertensive patients with impairment of renal function or subjects with underlying renal hypertension.

Numerous monoamine oxidase inhibitors (including iproniazid, 1-phenyl-2-hydrazino propane, phenelzine, and nialamide) have demonstrated significant antihypertensive effects.[10] Although the hypotensive effect obtained with these agents is predominantly orthostatic, a significant reduction in blood pressure is often obtained in the supine position as well. As with other potent antihypertensive drugs, it has been shown that the effect of these compounds is significantly enhanced by the accompanying administration of potent oral diuretics. However, the clinical use of MAO inhibitors in the treatment of hypertension has been limited until recently, mainly because the available

Table III. Response of blood pressure to methyl dopa, guanethidine, and pargyline when given alone and in combination with hydrochlorothiazide

	Number of patients	Supine				Erect			
		Normotensive*		Mean blood pressure reduced > 20 mm. Hg or normotensive		Normotensive		Mean blood pressure reduced > 20 mm. Hg or normotensive	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Methyl dopa	38	6	16	13	34	9	24	16	42
Methyl dopa plus hydrochlorothiazide	19	8	42	12	63	10	53	17	89
Guanethidine	30	5	17	12	40	13	43	27	90
Guanethidine plus hydrochlorothiazide	25	6	24	13	52	14	56	22	88
Pargyline	33	5	15	7	21	19	57	27	82
Pargyline plus hydrochlorothiazide	11	1	9	4	36	5	45	9	82

*Blood pressure reduced to 140/90 mm. Hg or less.

compounds with the greatest antihypertensive effectiveness had a significant incidence of accompanying side reactions. The introduction of the nonhydrazine MAO inhibitor pargyline appears to provide a clinically effective antihypertensive drug with a relatively low incidence of side reactions.

The present study indicates that oral pargyline is a potent antihypertensive agent. The hypotensive effect obtained is predominantly orthostatic; however, a reduction in blood pressure often occurs in the supine position as well. As with other potent antihypertensive drugs, the concomitant use of an oral diuretic increases the supine response, reduces the dosage requirement of the drug, and thereby decreases the incidence of accompanying side reactions.

The over-all incidence of accompanying side reactions with pargyline is small but significant. The occurrence of dry mouth, constipation, impotence, and blurred vision suggests the possibility of accompanying parasympathetic blockade. Although a significant gain in weight was noted in several instances, clinically evident edema did not occur. Since the coadministration of hydrochlorothiazide did not correct or prevent the gain in weight, it seems likely that retention of sodium and water was not responsible for the gain in weight. Hence the possibility of an anabolic effect attributable to the pargyline must be considered.

Over-all, the clinical characteristics of pargyline are sufficiently favorable to recommend its application in the treatment of severe diastolic hypertension. The comparative clinical responses recorded in Table III indicate that pargyline and guanethidine provide greater antihypertensive effectiveness than does methyl dopa when these agents are used singly. In order to achieve maximum antihypertensive effect and avoid excessive orthostatic hypotension, careful dosage titration is required with each of these drugs.

Summary

Pargyline is a potent antihypertensive drug with a predominantly orthostatic antihypertensive effect. The accompanying use of a thiazide diuretic increases the response in the supine position, reduces the dosage requirement of the drug, and thereby decreases the incidence of accompanying side reactions.

The antihypertensive potency of pargy-

line is similar to that of guanethidine and both are more potent than methyl dopa when these agents are used singly In contrast with the cardiac hemodynamic response elicited by guanethidine neither pargyline nor methyl dopa reduces cardiac output On the other hand methyl dopa has a more beneficial renal hemodynamic effect In general pargyline and guanethidine can be recommended for severe hypertensive situations whereas methyl dopa has greater application in less severe hypertensive states and in cases of renal hypertension

The various drugs used in this study were kindly supplied by the following pharmaceutical companies pargyline (Eutonyl) by Abbott Laboratories methyl dopa (Aldomet) and hydrochlorothiazide (Hydro Diuril) by Merck Sharp & Dohme and guanethidine (Ismelin) and hydrochlorothiazide (Esidrix) by Ciba Pharmaceutical Company

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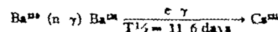
The direct diagnosis of myocardial infarction by photoscanning after administration of cesium-131

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In view of the clinical importance of myocardial lesions a technique for visualizing them in the intact patient is clearly desirable The advent of scintillation scanning suggested a promising approach to this problem The first encouraging result was the finding that dogs with experimental myocardial infarcts showed less concentration of rubidium 86 in the area of infarction than in normal myocardium[1] This permitted clear visualization of the infarct if the heart were subsequently removed from the dog but the high energy of the gamma emission of rubidium 86 made it unsuitable for studies of the heart in situ The next step demonstration of experimental myocardial infarcts through the intact chest wall of the living animal was first successfully accomplished by the use of mercury 203 labeled chlormerodrin[2] When applied to human beings however this technique proved to be only irregularly successful The development of a method for obtaining suitable quantities of cesium 131 for use in human beings has now permitted the use of the latter isotope in myocardial scanning The present communication demonstrates the usefulness of cesium 131 in experimental myocardial infarcts in dogs and in myocardial infarcts in human beings

Methods

Preparation of cesium 131 Cesium 131 was prepared in a nuclear reactor by neutron irradiation of barium Barium 130 a stable isotope present in natural barium to the extent of only 0 1 per cent reacts to produce barium 131 which in turn decays to produce cesium 131



$$Ba^{130}\ (n\ \gamma)\ Ba^{131} \xrightarrow[T^{1/2} = 11\ 6\ \text{days}]{\epsilon\ \gamma} Cs^{131}$$

Despite the low isotopic abundance of barium 130 the combination of a ten barn cross section of the isotope and a high flux irradiation makes it possible to produce reasonable amounts of cesium 131 As barium 131 decays with a half life of 11 6 days to cesium 131 the former isotope may be reprocessed periodically for the extraction of cesium 131

Cesium was separated from the cesium barium mixture by the use of a weakly acidic carboxylate type cation exchanger in the ammonium form Barium exhibits a high affinity for this exchanger when ap

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plied at a pH of 6 to 7. Cesium was then eluted using a 0.15N ammonium acetate buffer at pH 6. Cesium 131 has a half life of 9.71 ± 0.05 days and decays exclusively by orbital electron capture directly to the ground state of xenon 131. The 29.4 kev. xenon x-ray resulting from K capture is the only radiation detectable with conventional sodium iodide detectors. The absorption of the 29.4 kev. x-ray in water has a half value of approximately 2.4 centimeters. Cesium 131 was administered to patients and experimental animals in the form of a sterile carrier-free solution of the sulfate, chloride, or acetate, adjusted for isotonicity by the addition of sodium chloride.

Studies in dogs. Twenty-seven dogs received cesium 131 intravenously in doses of 40 to 650 μc. In preliminary work, 8 additional dogs received 250 to 500 μc of cesium 134 intravenously. Of the 35 dogs studied, 15 were used in preliminary work for information on scanning techniques, tissue uptake, etc. Each of the other 20 (10 dogs subjected to coronary artery ligation, 3 control dogs with sham operations, and 7 dogs without operations) underwent complete studies according to the protocol previously described.[8] In this protocol, experimental myocardial infarcts were produced by ligation of the anterior descending branch of the left coronary artery. After closure of the chest and recovery, the dogs were studied 1 to 57 days after operation. At the time of study, each dog received cesium 131 and was scanned in the supine position at intervals ranging from 1 hour to 3 hours after injection of the isotope. A commercial scanner* with a 19 hole focusing collimator and 3 inch crystal was used. The focus point of the collimator was 7 cm. from its face. At the conclusion of the scan, the animal was sacrificed and the heart transfixed by long needles driven through the anterior chest wall. The anterior chest wall was removed and the exact projection of the cardiac outlines placed on the scan. The heart was then excised, emptied of blood, and rescanned. Sections of tissue from liver, myocardium, and other thoracic organs were then taken for the determination of radioactivity in a well counter. Myocardial sections were subsequently sent to a pathologist for histologic examination. Wherever subsequent reference is made to infarcted or normal canine myocardium, the status of the tissue has been verified in each case by microscopic examination. Thus, except for the use of radioactive cesium in the present studies, the protocol followed in detail that previously described for the use of mercury 203 chlormerodrin.

Studies in man. On the basis of the results obtained in dogs, 13 patients received 1.1 to 2.5 mc. of cesium 131 intravenously; in the majority the dose was 1.25 mc. The estimated radiation dose (whole body) was 400 millirads. Two and three quarters hours after injection, each patient was scanned in the supine position using another scanner of the same model as that employed in dogs. The 19 hole collimator was placed approximately 1.5 cm. above the chest wall. Before scanning took place, the precordial area was scouted by manually moving the probe over various parts of the heart to establish the point of maximum count rate. Except in the case of a posterior infarct, this area was usually found 5 to 6 cm. above the xiphoid and about 3 cm. to the left of the midsternal line. It was necessary to exercise care in order to avoid confusing the high count rate obtained over the liver with counts from the myocardium.

After the maximum myocardial count rate had been obtained, the scanner voltage was set to produce maximum density of the film at this count rate. The scanner was adjusted for sharp contrast.* Scans were begun at the xiphoid and were extended cephalad to approximately the lower level of the second rib. The field of the scan extended laterally from the body wall on the left side to a line approximately 7 cm. to the right of and parallel to the midsternal line. By observation of the dot scan, it was usually possible to readjust the lateral margins of the scan after the first several lines had been recorded, bringing the margins in and permitting faster completion of the scan. Scans were usually

*Magnascanner, Picker X-ray Corp., White Plains, N. Y.

*With the Picker scanner [illegible] the [illegible] differential [illegible] was set at 15. With other [illegible] scanners [illegible] setting would be [illegible] appropriately [illegible]

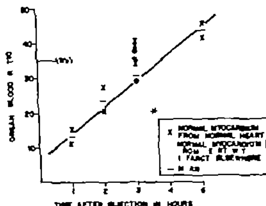


Fig 1 Uptake of cesium 131 by normal canine myocardium. Each point represents normal myocardium from an individual dog The organ blood ratio is the ratio [cesium 131] in myocardium/[cesium 131] in blood of the same animal Note that the dots refer to normal myocardium from heart having infarcts elsewhere in them whereas the other points represent myocardium from entirely normal hearts

performed at a speed of 16 cm per minute with a spacing of 0 45 cm between lines The scans took approximately 50 minutes to complete Patients were brought in their beds to the Nuclear Medicine Unit and scanned without the necessity of moving from their beds at any time When each patient had subsequently recovered sufficiently from his infarct to permit chest x ray examination a film was taken and the cardiac silhouette projected onto the scan with appropriate corrections for difference in focus Since the heart x ray film was taken with the patient in the upright position the projection of the cardiac outline on the scan could not be exact Although not necessary for the reading of the scan this crude method of superimposition made orientation of the scan somewhat easier

The 13 patients were classified before scanning as follows (a) 6 had suffered *unequivocal acute myocardial infarction* 2 to 16 days previously (b) 2 had suffered *probable recent acute myocardial infarction* (c) 2 had heart disease but had *probably not suffered recent myocardial infarcts* (d) 3 were *control patients without any evidence of heart disease* Each of the 6 patients with unequivocal recent infarction met all three of the following criteria a classic history of recent acute infarction clearly diagnostic electrocardiographic changes and elevation of serum glutamic oxaloacetic transaminase or lactic dehydrogenase activities above normal Each of the 3 control patients met all of the following criteria no history suggestive of heart disease no physical findings indicating heart disease normal appearance of the heart on an x ray film of the chest and normal electrocardiogram Each control patient was over 40 years old thus placing the controls in the same general age group as the patients with acute infarction The 4 patients in the two intermediate classes (Groups b and c) are further described below

Results

Dogs The normal myocardium of the dog showed a rapid uptake of radioactive cesium Two hours after injection the myocardium contained 20 times as much radioactivity per gram as whole blood Normal myocardium from dogs with an infarct elsewhere in the heart showed no significant difference from normal myocardium obtained from entirely normal hearts (Fig 1) However these studies were designed primarily to provide a background for developing a scanning technique the more careful clearance studies of Levy[4] have suggested that ligation of a branch of the coronary artery increases the uptake of rubidium 86 by areas of myocardium supplied by unoccluded vessels No other thoracic tissue showed sufficient

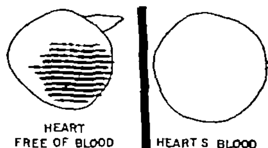


Fig 2 Absence of detectable radioactivity in heart blood scanned simultaneously with the heart from which it had been taken. On the left the cesium 131 in the myocardium is clearly detected by the photoscan whereas the entire content of heart blood emptied into a beaker is not visualized Both the emptied heart and beaker of blood were scanned simultaneously the scanner settings being the same for both

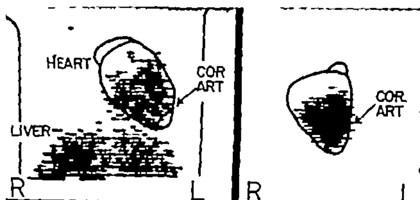


Fig 3 Normal canine myocardial scan On the left the scan of the beating heart of the living dog through the intact chest wall On the right the isolated heart of the same dog emptied of blood and rescanned That portion of the anterior descending branch of the left coronary artery that was visible when the chest was opened is shown in projection on the scan

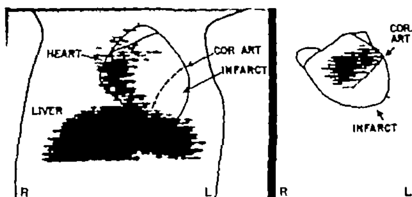


Fig 4 Extensive anterior myocardial infarct in a dog On the left the scan of the intact dog shows a large cold area corresponding to the infarct This is confirmed by the scan of the isolated heart on the right There was extensive necrosis in the area indicated by the scan

uptake of cesium to interfere with the myocardial scan However the liver showed appreciable uptake and the ratio of hepatic uptake to myocardial uptake increased with time The optimum time between injection of cesium 131 and performance of a myocardial scan is therefore a compromise between two factors the longer the time between injection and scanning the higher the myocardial uptake relative to the blood the shorter the time between *injection* and scanning the higher the myocardial uptake relative to the liver The optimum time to begin the scan appeared to be 2 to 3 hours after injection At that time the concentration of radioactive cesium in the myocardium is approximately twice that in the liver and approximately 20 times that in the blood The latter value should permit demonstration of the myocardium without detection of any radioactivity from the blood contained within the heart cavity As a further proof of the latter point one dog was sacrificed one and two thirds hours after the injection of radioactive cesium and all the great vessels to the heart were clamped thus trapping within the heart the entire diastolic contents of the heart cavities A needle was then *introduced* through the myocardium and all the blood was evacuated from the heart This entire volume of blood was placed *in* a beaker The emptied heart and the beaker of

blood were then scanned in a single scan the same scanning factors applying to each The result (Fig 2) showed a clear outline of the empty left ventricle whereas the beaker of blood gave no detectable radioactivity with this technique

The normal left ventricular myocardium of the dog was well delineated in scans taken 2½ hours after the administration of 150 to 650 μc of cesium 131 Fig 3 shows such a normal scan On the left the scan obtained from the beating heart

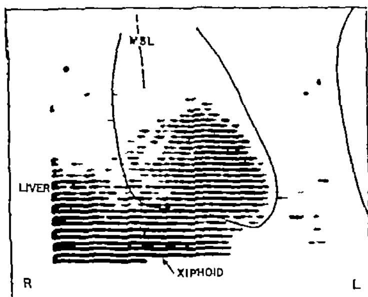


Fig 5 Normal myocardial scan in a 52 year-old man The left ventricle is visualized through the thinner overlying right ventricle the latter is not visualized because of its lesser mass The outline of the heart shadow was projected onto the scan from a separately taken x ray film MSL Mid-sternal line

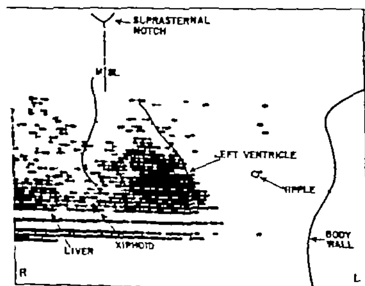


Fig 6 Normal myocardial scan in a 61 year-old woman

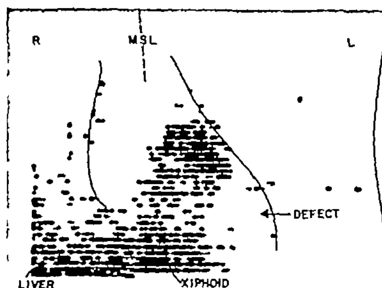


Fig. 7. Anterior myocardial infarct in a 59-year-old man scanned 3 days after the acute episode of infarction. (In Figs. 7 through 11 the stated location of the infarct is that demonstrated by the electrocardiogram.)

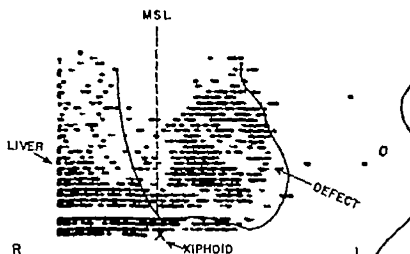


Fig. 8. Anteroseptal infarct in a 66-year-old woman scanned 2 days after the acute episode.

of the living dog through the intact chest wall is shown. The full, even density of the left ventricle appears through the thinner overlying right ventricular wall. Although the concentration of cesium in the right ventricle and atrium is the same as that in the left ventricle, only the thicker left ventricular mass is detected by the scan. This myocardium is shown again in the isolated heart emptied of blood on the right. By spreading out the opened heart and scanning it we were able to confirm that the scan shows the thicker left ventricle and does not show the thinner right ventricle or atria. Myocardial infarcts were clearly shown as cold areas of decreased uptake. Fig. 4 shows a large anterior infarct. The decreased uptake in infarcts was confirmed by tissue counting. Since the experimental infarcts were al-

ways in the anterior left ventricular wall the posterior left ventricular wall (supplied by the unligated circumflex branch) served as a normal tissue for comparison In 7 dogs the concentration of cesium 131 in samples of myocardium in which the infarction was confirmed by histologic examination was 25 1 per cent (range 7 9 to 42 1 per cent) of that present in the normal left ventricular myocardium of the same dogs *The low* uptake in infarcts was due to infarction and not to the fact that the tissues came from the anterior wall of the left ventricle for in control dogs the concentration of cesium in the (normal) anterior left ventricular wall did not differ significantly from that in the normal posterior left ventricular wall Sham operated control dogs did not differ from unoperated control dogs either in scans or tissue counts

In some dogs tissue in the area supplied by the anterior descending branch of the left coronary artery failed to develop

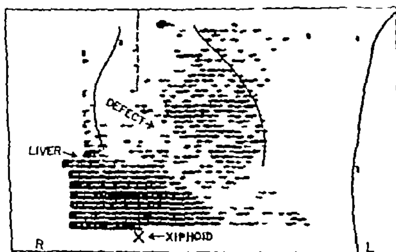


Fig. 9 *Doubtful* scan of a posterior infarct in a 50-year-old man scanned 10 days after the acute episode The patient had no evidence of pericardial fluid and a definite friction rub was audible at the time of scanning

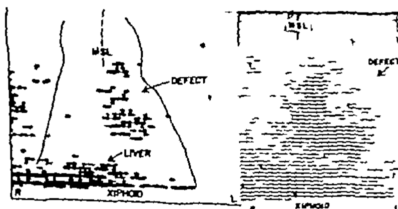


Fig. 10 High anterolateral infarct in a 51 year-old man scanned 16 days after the acute episode The photoscan on the left should be compared with the dot scan on the right. The separation between hepatic and myocardial densities represents pericardial fluid in this patient The high lateral "cold" area of infarction is also clearly seen as indicated by the arrow A ventricular aneurysm was subsequently demonstrated by angiography in the latter area

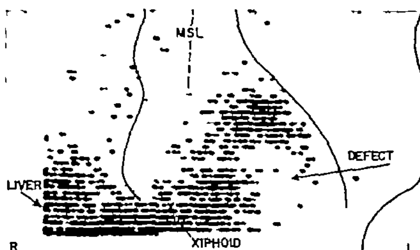


Fig 11 Anterior infarct in a 68 year-old woman scanned 14 days after the acute episode The electrocardiogram showed evidence of a previous infarct but did not detect the fresh infarct

frank necrosis even after ligation of this artery As previously described[2] such tissue has been arbitrarily classified as ischemic The mean concentration of radioactive cesium in such ischemic tissues in 6 dogs was 65 6 per cent (range 19 7 to 99 4 per cent) of that in normal left ventricle of the same dogs Thus ischemic tissue showed an uptake of cesium less than that of normal tissue but greater than that of infarcted tissue

Although our data do not yet permit a definite statement about the relationship between cesium uptake and the time that has elapsed since infarction areas of infarction tended to have a very low concentration of cesium in dogs given the isotope 1 day after infarction whereas *there was a tendency toward somewhat* higher concentrations in dogs which received cesium at later times But the concentration of cesium in scar tissue in the 57 day old infarct was also very low Areas of ischemia showed low concentration when the isotope was given during the first few days after ligation with fairly prompt recovery toward normal uptake by the fifth day

Human beings Fig 5 shows a normal myocardial scan obtained in a male control patient The smooth curved outline of the ventricular myocardium is apparent The diaphragmatic surface of the heart is closely adjacent to the area of hepatic uptake Fig 6 shows another normal scan obtained in a female control patient Whereas our method of projecting the cardiac silhouette onto the scan in dogs should insure accurate placing of the outline on the scan the cardiac silhouette in human beings was obtained from a separately taken chest x ray film as noted above and therefore minor discrepancies between the cardiac silhouette and the exact border of the scan density are not significant

Figs 7 8 9 and 10 show scans from patients who had previously been classified as having *unequivocal fresh myocardial infarcts* (see above) Fig 7 shows a large cold area of decreased uptake involving much of the apical and anterolateral walls of the left ventricle a location entirely *consistent with the electrocardiographic* findings in this patient Fig 8 shows a fresh anteroseptal infarct the defect extends obliquely to the margin of the ventricular density This location was consistent with the electrocardiographic findings Our experience in dogs and in patients suggests that infarcts may be generally more easily detectable in the early days after infarction than during the second week This fact may be significant in the scan shown in Fig 9 This scan taken 10 days after an acute posterior infarction (as located electrocardiographically) was read as doubtful Although the crescentic area of decreased uptake in the diaphragmatic portion of the left ventricle breaking

the normal contour suggests an infarct and although this location is consistent with the electrocardiographic localization the scan was not considered to be definitely positive This scan was the only doubtful scan obtained in the 6 patients with unequivocal infarcts The patient whose scan is shown in Fig 9 had no evidence suggestive of pericardial effusion at the time of the scan and indeed he had a marked friction rub at that time Fig 10 is a scan obtained in a patient with electrocardiographic evidence of a fresh high anterolateral infarct At the time of the scan he was also known to have a pericardial effusion An examination of the photoscan shown on the left and the dot scan shown on the right clearly reveals the defect due to the infarct located high and laterally The separation due to the accumulation of pericardial effusion causes a defect that is much less striking than one due to the infarct Moreover the relatively cold area between the heart and liver in this instance does not show any definite break in the smooth contour of the myocardium This patient developed a ventricular aneurysm as proved by angiography in the area of recent infarction

Of the 6 patients with unequivocal recent acute myocardial infarcts (Group a) the scans were positive in 5 and doubtful in 1 (Fig 9) All 3 of the control patients (Group d) gave clearly negative scans

Among the 4 patients in the two intermediate classes (Groups b and c) whose clinical status was not unequivocally established the results were as follows A patient who had had an anteroseptal infarct in 1961 and severe angina since January 1963 was admitted to the University Hospital in March 1963 with the clinical diagnosis of a fresh infarct Serial changes in serum enzyme activities supported the clinical opinion and placed the date of the infarct about March 14 The electrocardiogram showed evidence of old infarction but no evidence of recent infarction A scan taken on March 28 clearly showed a large anterior infarct (Fig 11) In a second patient a 56 year old man with a history of old infarction angina and a recent clinical diagnosis of acute myocardial infarction the clinical diagnosis was supported by changes in serum enzyme activities but the electrocardiogram did not show diagnostic changes The scan was read as negative Thus in the 2 patients who had probable but not certain acute infarcts (Group b) the scan was positive in one and negative in the other

In Group c a 55 year old man had aortic stenosis, left ventricular hypertrophy no history of angina and no electrocardiographic evidence indicative of myocardial infarction Cardiac catheterization and angiography had documented the aortic stenosis and had also shown stenosis of the left coronary artery without any evidence of complete occlusion The scan was negative The other patient in this group was a 72 year-old man with severe angina hypertension and congestive failure Neither his electrocardiogram nor his history suggested any definite recent infarction The scan was read as doubtful

Discussion

Now that the use of cesium 131 has permitted successful visualization of infarcts in living patients the possible uses of this technique may be considered Accurate localization of infarcts by direct visualization is now a reasonable hope Diagnosis of myocardial infarcts in patients with a doubtful history or electrocardiogram has probably been possible in at least one patient (Fig 11) But we have deliberately chosen to evaluate the new technique chiefly by comparing unequivocal normal hearts with unequivocal infarcts It was thought that this would lead to the most rapid determination of the validity of the test Nevertheless one is obviously more likely to turn to the scan in cases in which the clinical findings and electrocardiogram conflict than in cases in which there is no such conflict Therefore subsequent evaluation of myocardial scanning should probably include studies of doubtful cases in which only necropsy findings will permit final evaluation

We cannot yet say what value if any the scan will have in patients who are thought to have impending myocardial infarction or in the evaluation of patients with angina pectoris We suspect that it will be more difficult to distinguish between the chronically ischemic myocar

dium and the myocardium with an acute infarct than to distinguish between the chronically ischemic myocardium and the normal myocardium Thus the scan may turn out to be useful in puzzling cases of severe heart pain The possible usefulness of the myocardial scan in certain other disorders e g myocarditis remains to be evaluated Although the suggested use of I^{131} as iodide to demonstrate myocardial infarcts[5] proved to be disappointing[6,7] Evans[8] has indicated the feasibility of demonstrating infarcts by heart scans after the administration of radioiodinated fatty acids this interesting approach also deserves to be evaluated in disorders such as myocarditis

The scan might theoretically offer the possibility of directly showing the thickness of the left ventricular wall but one must be cautious in this regard The technique of myocardial scanning has been deliberately arranged in such a way as to produce a full even density in the normal heart without showing the left ventricular cavity If one changes the technique in order to bring the left ventricular cavity into focus then one has the possibility of misinterpreting the left ventricular cavity as a cold area of infarction With proper attention to the setting of the scanner it has been found quite easy to avoid mistaking the normal left ventricular cavity for a cold area especially if one remembers that large infarcts tend to reach the *outer surface of the myocardium in one or* more areas of the scan This conservative method of reading is recommended in order to prevent false positive diagnoses of myocardial infarction It is admitted *that* such *conservatism will probably* sacrifice our ability to detect left ventricular hypertrophy and quite possibly our ability to detect subendocardial infarcts

Summary

1 It is possible to visualize the left ventricular myocardium of the intact living patient without discomfort or danger to the patient, by photoscanning after the administration of cesium 131

2 The normal left ventricular myocardium appears as a full even density with a smooth contour Myocardial infarcts appear as cold areas of decreased uptake

3 In 6 patients with unequivocal fresh myocardial infarcts the scans were positive in 5 and doubtful in 1 In 2 patients who probably had suffered recent myocardial infarctions the scan was positive in 1 and negative in 1 In 2 patients who had heart disease but who had probably not had recent myocardial infarctions the scan was negative in 1 and doubtful in 1 The scan was negative in each of 3 patients with normal hearts

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Genesis of the electrocardiogram in atrial septal defect

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The need for a more basic understanding of the pattern of myocardial excitation in specific forms of ventricular hypertrophy is especially important in view of the increasing clinical application of the electrocardiogram in the evaluation of congenital heart disease. The maximum value of the electrocardiogram as a diagnostic implement will be realized when it is interpreted in light of the knowledge of the events of ventricular activation.

In the lesion of atrial septal defect, the mechanisms responsible for the abnormal electrocardiographic features remain largely speculative. Burch and DePasquale[1] and others[2] have noted that although the electrocardiographic pattern in cases of atrial septal defect is suggestive of right bundle branch block, the mechanism for the pattern apparently is not interference with conduction of the impulse through the right bundle branch. Martins de Oliveira and Zimmerman[4] suggested that the primary abnormality is late activation of the basal portion of the right ventricle and interventricular septum. Burch and DePasquale[1] have emphasized that the late vectors of ventricular depolarization originate from the hypertrophied crista supraventricularis.

This investigation was conducted to (1) determine the sequence of ventricular activation in dogs with surgically created atrial septal defects, (2) correlate the events of ventricular depolarization with the vectorcardiographic tracing, and (3) determine the presence or absence of interference with conduction of the impulse through the right bundle branch, the peripheral conduction system, and the muscle of the right ventricle.

Methods

In 10 dogs which weighed between 15 and 30 kilograms, a thoracotomy was performed in the fourth right intercostal space and an atrial septal defect was created through the right atrium during inflow occlusion of the venae cavae as described by Bowes and associates.[5] A control group of 5 dogs underwent a similar surgical procedure, including right atriotomy, but no atrial defect was created. The electrocardiogram was monitored throughout the procedure, and there was no evidence of interventricular conduction

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Fig. 1. Arterial dye-dilution curve in a dog with atrial septal defect. Similar curves were recorded in all dogs with surgically created atrial septal defects. The left-to-right shunt in this group comprised 65 to 81 per cent of total pulmonary blood flow, as calculated by the method of Carter and co-workers.[14]

disturbance or heart block. All of the dogs in the control group survived the operation; however, 5 of the dogs with atrial defects died in congestive heart failure 1 to 2 weeks postoperatively. Necropsy showed large atrial defects and marked dilatation of the right ventricle in these animals.

Monthly electrocardiograms were obtained, and when it was considered that significant electrocardiographic changes had developed (7 to 11 months postoperatively), cardiac catheterization was performed. Each dog was anesthetized with intravenous pentobarbital, 30 mg. per kilogram. Polyvinyl catheters were passed into the pulmonary artery via the right jugular vein and into the left ventricle via the right femoral artery. Arterial dye-dilution curves (Fig. 1) were obtained using a Waters XP 250B densitometer with indocyanine dye (Cardiogreen). Injections were made into the right atrium, right ventricle, and left ventricle while sampling was done through a needle in the left femoral artery. Pulmonary and systemic blood flows were calculated by the methods of Moore and co-workers[9] and Carter and associates.[14] Statham transducers were used for measurement of pressures, and all catheterization data were recorded with a Heiland Visicorder oscillograph.

Vectorcardiograms were recorded preoperatively and at the time of the study of ventricular activation in the control dogs as well as in those with atrial septal defects. All recordings were taken with the dog in a right lateral decubitus position. The equilateral tetrahedron reference system was used with the Sanborn 185 Vector Amplifier and Viso-Scope. The beam was interrupted at 0.0025 second for timing purposes. Scalar tracings of X, Y, and Z leads were recorded from the oscilloscope.

Ventricular activation. The multipolar electrodes were of the type used by Scher and co-workers.[11] Each electrode consists of 15 fine insulated tungsten wires assembled around a central shaft. The ends (uninsulated) of the recording wires are approximately 1 mm. apart, with a 0.3 mm. maximal diameter of the assembly. The multipolar electrode was connected to 12 Type 122 Tektronix preamplifiers in series with Honeywell power amplifiers which drive M 1650 fluid-damped miniature galvanometers of a 12 channel Visicorder oscillograph. The frequency response of the recording system is flat to 1,000 cycles per second. All records were obtained at a paper speed of 500 mm. per second. Unipolar (each terminal against a distant electrode) and bipolar (difference between adjacent points) tracings were recorded by means of appropriate switching apparatus which allows recording from 15 electrode points on channels 1-10. The deflection of the bipolar record indicated the direction of spread of activity (Fig. 4), and the convention used here was that described by Scher (a negative deflection indicates spread away from the tip of the electrode).[11] Throughout each experiment a Lead II electrocardiogram was monitored on channel 12, and a fixed time reference bipolar lead in the left ventricle was recorded on channel 11 (Fig. 4).

The 5 control dogs and 5 dogs with atrial septal defects were studied 8 to 12 months postoperatively (1 month after cardiac catheterization). Each dog was anesthetized with intraperitoneal pentobarbital, 30 mg. per kilogram, and artificial respiration was administered via a tracheostomy tube. The chest was opened with a longitudinal sternum-splitting incision, and the heart was cradled in the pericardium. The reference electrode was inserted into the left ventricle, and a base-line tracing was recorded. Twenty to 30 electrodes were inserted into each heart. Initial insertions were placed in the free wall of both ventricles. They were subsequently pushed into the septum and crista supraventricularis. Electrode insertions into the

free wall of the outflow tract of the right ventricle were carefully positioned so that they could be placed into the crista and high septal areas. The activation of the low right septum was recorded last because of the possibility of inducing right bundle branch block with such insertions. In 1 dog, the experiment was terminated after 20 insertions because the configuration of the Lead II tracing changed.

At the conclusion of each experiment the electrodes were passed completely through the heart, a fine thread was attached to the electrode and it was withdrawn through the heart for identification of electrode tracts. The endocardium was stained with Lugol's solution and photographed.[12] Measurements of the thickness of the ventricular walls and of the dimensions of the atrial defects were recorded.

Methods of analysis

I. VENTRICULAR ACTIVATION. The identification of local activation times of bipolar records was taken as the peak or nadir of monophasic complexes. With diphasic complexes, the instant at which the intrinsic deflection crossed the isoelectric line was used. Durrer and van der Tweel[13] have discussed in detail the criteria for acceptance of such tracings. Approximately 5,000 measurements from 133 insertions form the basis of the results presented. The local activation times were used to construct isochronous planes according to the method of Scher and associates[11] to demonstrate the sequence of ventricular excitation. All local activation times were related to the timing of the reference electrode.

To correlate the sequence of ventricular activation with the vectorcardiographic tracing, the following procedure was used: (1) The local activation times were measured with respect to the bipolar reference electrode. (2) The timing of the reference electrode in turn was identified with respect to the peak of the R wave of Lead II (channel 12). Measurements were performed for each electrode insertion, and the interval from the deflection of the reference electrode to the deflection of the peak R wave of Lead II did not vary more than 2.0 msec. (3) The nadir of the Y lead of the vectorcardiographic scalar tracing was identified as coinciding in time with the peak of the R wave of Lead II.

II. QUANTITATIVE VECTORCARDIOGRAPHY. Timing components of the QRSsE loop were initially identified from the scalar tracings of the X, Y, and Z leads. The magnitudes of the spatial Q, R, and S vectors were calculated according to the Pythagorean theorem by substituting the projections of each vector Ex, Ey, and Ez into the formula

$$sE = \sqrt{Ex^2 + Ey^2 + Ez^2}$$

The identification of the Q, R, and S loops was performed according to the method of McCall and co-workers.[14]

Results

I. Hemodynamic studies. The 5 dogs which survived surgical creation of an atrial septal defect appeared to be dyspneic for 4 to 7 days postoperatively, and thereafter were in good condition. Cardiac catheterization data, obtained 7 to 11 months postoperatively, are presented in Table I. Pulmonary arterial pressures were moderately elevated (mean pressures 30 to 36 mm. Hg). Right ventricular systolic pressures varied from 40 to 56 mm. Hg and no systolic pressure gradient was demonstrated between the right ventricle and pulmonary artery. Right and left ventricular end-diastolic and right atrial pressures were normal. Aortic pressures were elevated (mean pressures 120 to 150 mm. Hg) as noted in most normal dogs studied in our laboratory with the use of pentobarbital anesthesia.

Total pulmonary blood flow varied from 4.2 to 15.2 liters per minute, and systemic cardiac output (1.5 to 2.9 liters per minute) was within normal limits for our laboratory. The smallest systemic and pulmonary blood flows were found in the smallest dog (body weight of 15 kilograms) of the series. The percentage of pulmonary blood flow comprised by the left-to-right shunt, as calculated from arterial dye-dilution curves (Fig. 1), varied from 65 to 81 per cent.

II. Vectorcardiographic studies

A. CONTROL GROUP. Quantitative analysis of the QRSsE loop was performed for tracings made preoperatively and 7 to 8 months postoperatively. This was done to

*Table I Summary of catheterization data in 5 dogs with atrial septal defects**

	Range of values
Weight (kg)	15–30
Pressure (mm Hg)	
Right atrium	5/1 – 7 5/3
(Mean)	3 6
Right ventricle	40/6 – 56/3
Pulmonary artery	40/18 – 56/25
(Mean)	30 – 36
Left ventricle	145/10 –1 3/12
Aorta	145/110–173/131
(Mean)	120 150
Blood flow (L /min)	
Systemic	1 5– 2 9
Pulmonary	4 2–15 2
Left to-right shunt	2 7–12 3
Pulmonary flow comprised by left to right shunt (%)	65–81

*C [illegible] catheterization was performed 7 t 11 m th post operatively Each st dy was perf rmed with the d g in right lateral decub tus p sit on [illegible] [illegible]

determine whether the surgical procedure alone produced electrocardiographic changes The results are presented in Table II The data were analyzed for the dogs as a preoperative and postoperative group as well as paired data for each animal There was an excellent correlation (p = 99 per cent) for the spatial magnitude of the Q R and S portions of the QRS-E loop for the tracings obtained before and after operation The QRS duration varied from 33 to 36 milliseconds (msec)

B ATRIAL SEPTAL DEFECT GROUP All dogs developed electrocardiographic changes (enlargement of S waves in Leads II III and aV_F) 3 to 7 months postoperatively A detailed analysis of the quantitative vectorcardiographic changes was limited to the S loop in the dogs with atrial septal defects The average preoperative spatial S was 0 44 mv (range 0 34 to 0 72 mv) and postoperatively the average was 1 17 mv (range 0 53 to 1 93 mv) This change resulted in a twofold to three fold increase in the magnitude of the S loop which was displaced superiorly and posteriorly Fig 2 B demonstrates the typical vectorcardiographic changes after the production of an atrial septal defect The QRS-E loop duration preoperatively was 33 to 36 msec and 7 to 11 months postoperatively it was 43 to 46 msec

III Ventricular activation studies

A CONTROL GROUP The results in the 5 normal dogs were in agreement with those in the studies of Scher and co workers[13] Fig 3 B summarizes the sequence of ventricular activation as determined from the construction of isochronous planes in a heart divided into four sections This pattern was the typical one for the normal dog The earliest points of activation consistently were found in the mid and lower

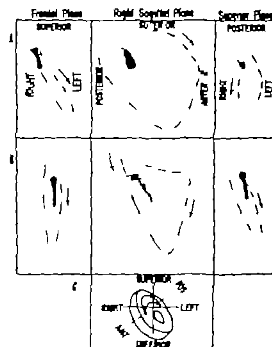


Fig 2 A Preoperative vectorcardiogram of a normal dog Quantitative analysis of the QRS F loop of the preoperative and postoperative tracings in the surgical control group showed no significant changes The equilateral tetrahedron reference system was used The QRS-E loop shown is the tracing obtained before creation of an atrial septal defect B Vectorcardiogram 8 months after surgical creation of an atrial sept l defect Quantitative analysis of the magnitude of the S loop demonstrated a twofold to threefold increase in the group w th atrial septal defect The S component was displaced in a superior direction C Anatomic orientation of the canine heart Note that the right (superior) and left (inferior) ventricles are oriented in a vertical direction In the canine heart the right ventricle is situated slightly posterior in relationship to the left ventricle

Table II Results of quantitative analysis of QRSsI loop in control group (preoperatively and postoperatively)

	Average				Range			
	Frontal plane		Sagittal plane		Frontal plane		Sagittal plane	
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop
A Axis of Q loop (degrees)	−39.5	−91	−55	−42	−63 to −140	−67 to −111	−10 to −47	−34 to −61
Voltage of Q loop (mv)	0.414	0.256	0.715	0.45	0.175 to 0.60	0.15 to 0.41	0.20 to 1.45	0.375 to 0.45
Time of Q peak (msec)	4.5	4.5			2.5 to 10.0	2.5 to 7.5		
Axis of R loop (degrees)	+65.6	+60	+66.4	+55	+55 to +77	+46 to +69	−56 to +77	+34 to +76
Voltage of R loop (mv)	1.917	1.756	1.846	1.792	1.31 to 2.7	1.175 to 2.9	1.3 to 2.35	0.99 to 3.235
Time of R peak (msec)	16.5	17.1			12.5 to 20	15 to 20		
Axis of S loop (degrees)	−35.8	−96	−130.5	−112	−40 to −111	−30 to −156	−101 to −134	−87 to −147
Voltage of S loop (mv)	0.361	0.546	0.138	0.308	0.175 to 0.85	0.01 to 1.05	0.2 to 0.90	0.05 to 0.915
Time of S peak (msec)	28.75	29.88			27.5 to 30.0	25 to 30		
QRS duration (msec)	34	34			33 to 37.5	33 to 37.5		

B

	Average	
Spatial Q (mv)		
Preop	0.58 ± 0.28	(p = 99)
Postop	0.41 ± 0.07	
Spatial R		
Preop	2.5 ± 0.60	(p = 99)
Postoperative	2.2 ± 1.25	
Spatial S		
Preop	0.64 ± 0.35	(p = 99)
Postop	0.65 ± 0.51	

C Atrial septal defect group

Spatial S	
Preop	0.11 mv (range 0.31 0.72 mv)
Postop	1.17 mv (range 0.54 1.91 mv)

[illegible] QRS [illegible] Q, R and S [illegible] QRS [illegible] significant differences between [illegible] pre [illegible] postoperative [illegible]

portions of the left side of the ventricular septum As shown in Fig 3 the early activation front (black area) during the first 7 msec occurred in the lower subendocardial areas of the left and right sides of the septum and in the apical portion of the left ventricle The wave front then moved in a circular fashion around both ventricular cavities in an apex to base direction (8 21 msec) *During this period invasion* of the septum occurred from both the left and right *surfaces in an apex to base* direction with the activation of the lower septum being completed by 21 to 25 msec

Several insertions into the papillary *muscles* demonstrated late activation of these structures relative to that of the left ventricular free wall Activation of the outflow tract of the right ventricular free wall and crista supraventricularis was completed by 25 msec Fig 4 *A* shows potentials recorded on one insertion of the multipolar electrode across the right ventricular free wall *adjacent to the pulmonary* valve A downward deflection resulted *from a negative potential in a* unipolar lead Right cavity potentials (points 1 7) from this area show a slight positive de

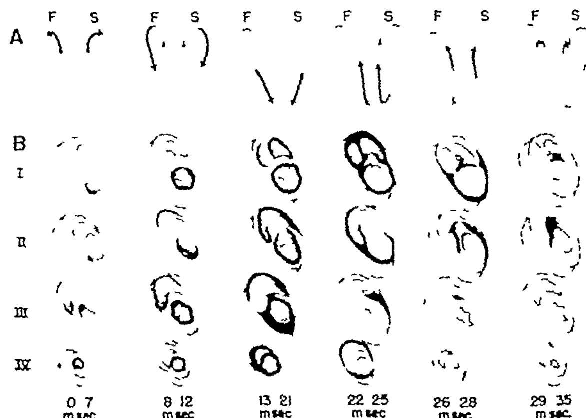


Fig 3 Correlation of the vectorcardiogram and the sequence of ventricular activation in a normal dog *A* The progressive inscription of the vectorcardiogram in the frontal (*F*) and right sagittal (*S*) planes The solid line represents that portion of the loop being inscribed during the time period indicated below (in milliseconds) *B* Pattern of myocardial activation in the normal dog The canine heart has been sectioned into four planes (*I II III IV*) from base to apex Progression of activation proceeds from left to right The black areas indicate the activation fronts for the time intervals shown The crista supraventricularis is indicated by the structure dividing the right ventricular cavity *in plane I* The *vectorcardiogram can be correlated with the activation* process during specified interval of time Note the following (1) *0 7 msec* Early septal activity the apical endocardial activity is associated with the inscription of the Q loop of the vectorcardiogram (2) *8 21 msec* Encirclement of ventricular cavities in an apex to-base direction with subsequent endocardial to-epicardial spread The wave fronts in the predominant left (inferior) ventricular mass are associated with the inscription of the R loop (3) *22 28 msec* Completion of activation of the free walls There was increasing predominance of right (superior) ventricular and basal excitation as the loop moved in a superior direction (4) *29 35 msec* Activation is completed by depolarization *of the basal septum* Note the *S loop inscribed* during this interval

flection before the dominant negative deflection. Points 8 through 10 show a prominent positive component followed by a rapid negative deflection indicative of local depolarization. In the bipolar record (Fig. 4 *B*) the slight deflection between points 1-2 indicates nearby septal activity and points 2-6 in the right ventricular cavity show no deflection. Points 7-10 show a downward deflection indicating activation from electrode tip to base, i.e., from the endocardium toward the epicardium. Note that the timing of the bipolar tracings indicates that this portion of the right ventricular free wall is activated during the peak of the R wave of the Lead II electrocardiogram. Calculation of the speed of conduction through the muscle of the right ventricular free wall showed that the spread of activity varied from 0.3 to 0.5 mm (average 0.41 mm) per millisecond. These results are in agreement with those of Scher and co-workers.[11]

Noteworthy aspects of the sequence of normal activation (Fig. 3) were: (1) double envelopment of the septum, with the occurrence of earliest activation on the left

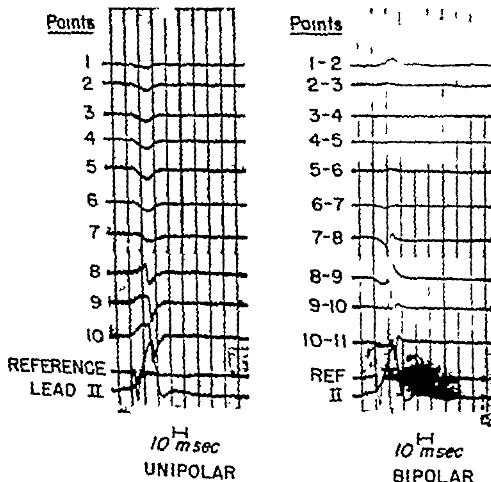


Fig. 4. Unipolar and bipolar tracings from an electrode insertion into the high right ventricular free wall in a normal dog. *Left* (*A*): The unipolar record shows a predominantly negative (downward deflection) from points 1 to 7 in the cavity. Points 8 to 10 in the free wall show a positive deflection (approaching activity) with a rapid negative deflection. *Right* (*B*): The bipolar tracings indicate local activation times. The deflection recorded between points 1 and 2 indicates nearby septal activity. Points 2 to 7 in the cavity show no deflection. Note that deflections from points 8 to 11 in the right ventricular free wall occurred during the peak of the R wave of Lead II.

side, (2) early activation of the apical portions of the ventricles with circular spread about both ventricular cavities and subsequent endocardial to epicardial activation of the ventricular free walls, (3) depolarization of the outflow tract of the right ventricle and *crista supraventricularis* by 25 msec, (4) occurrence of the latest activity in the basal portion of the ventricular septum, and (5) total ventricular activation time of 33 to 36 msec.

B. ATRIAL SEPTAL DEFECT GROUP. Total ventricular activation time was 43 to 46 msec, *as compared to the normal duration* of 33 to 36 msec. Figs. 5 and 6 show the sequence of ventricular activation in one dog and illustrate the typical pattern of activation of the group. The initial activation sequence was similar to that for *the normal group*, and the *earliest points* of depolarization were located in the middle portion of the left side of the *septum and lower anterior right septal surface*. Both septal surfaces began activation within the first 4 msec; the *earliest areas* were found on the left septal surface in 3 dogs and on the low right septal surface

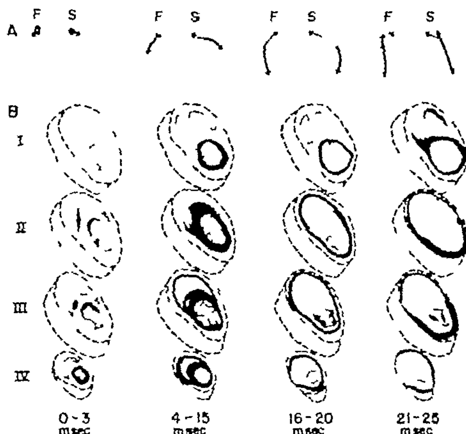


Fig. 5. (See also Fig. 6.) Correlation of the vectorcardiogram and the sequence of ventricular activation in a dog with atrial septal defect. *A*, Progressive inscription of the vectorcardiogram in the frontal (*F*) and right sagittal (*S*) planes. The solid line represents that portion of the loop being inscribed during the time period indicated. *B*, Pattern of ventricular activation (cf. Fig. 3). During the first 15 msec. the activation pattern is similar to normal. Activation of the crista supraventricularis occurred from 21 to 36 msec., whereas normally this area was depolarized during the interval of 17 to 23 msec. *The latest areas of activation (37-44.5 msec.) occurred in the free wall of the high* outflow tract of the right ventricle. Note that during inscription of the major deflection of the S loop (16-36 msec.) there was invasion of the crista and right ventricular free wall with receding activity in the left ventricle and basal septum. The terminal portion of the QRS-F loop (37-44.5 msec.) was related to completion of activation of the high right ventricular free wall.

in 2 The activation front then moved in a circular fashion as in the normal dog around both ventricular cavities in an apex to base direction (4 20 msec) During this interval there was double envelopment of the septum in planes II IV During the interval of 21 to 25 msec the activation front formed a circle encompassing both ventricular chambers in planes II and III Excitation of the left ventricular free wall was completed by 25 msec except in the high basal areas

Activation of the right ventricular free wall and crista supraventricularis occurred in the same sequence as in the normal dog however the total activation time was prolonged Figs 5 and 6 show that there was early activation of the anterior portion of the right ventricular free wall and right septal surface (planes III IV) in a normal sequence during the first 15 msec Also the subendocardial area of the right ventricular free wall and the crista supraventricularis were invaded by the activation front by 25 msec as occurred in the normal dog However invasion of the crista and high outflow tracts (plane I) began 2 to 4 msec later than normal and completion of activation of the crista and outflow tract of the right ventricle continued throughout the period of 26 to 36 msec Activation of the left ventricle and middle septum was completed during this interval Activation of the crista occupied the interval of 21 to 36 msec whereas in the normal dog this occurred during the period of 17 to 25 msec Ventricular activation was completed (37 44 5 msec) as the wave front moved to the epicardial surface of the high right ventricular free wall The latest sites of activation were in the subepicardial area of the free wall adjacent to the pulmonary valve

Fig 7 *A* shows potentials recorded from

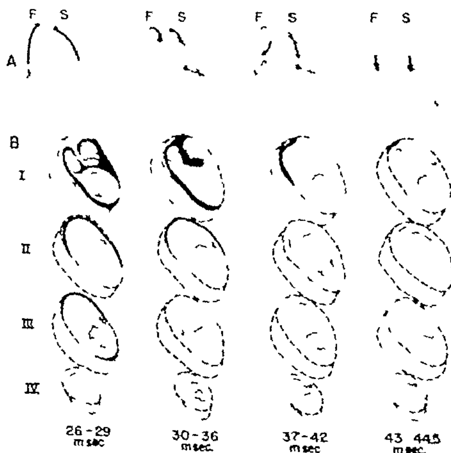


Fig 6 Same as Fig 5

the insertion of an electrode in the right ventricular free wall adjacent to the pulmonary valve. Point 1 is near the endocardial surface and point 10 is adjacent to the epicardial surface. Note the progressively more prominent upright deflection (approaching activity) and diminishing negative deflection (receding activity) from points 1 to 10. In the bipolar record (Fig. 7 *B*) points 1-2 were adjacent to the endocardial surface and points 10-11 were adjacent to the epicardial surface. The negative deflections indicate an endocardial to epicardial spread of activation. Also note that the timing of local activation from the bipolar record indicates that this portion of the free wall is activated during the latter part of the QRS deflection of the Lead II electrocardiogram. Fig. 4 *B* shows that a similar area of the normal heart activates during the peak of the R wave in Lead II.

Calculation of the speed of conduction through the muscle of the right ventricular free wall including the high outflow tract revealed this to vary from 0.3 to 0.5 mm (average 0.40 mm) per millisecond as found in the normal dog. Estimation of

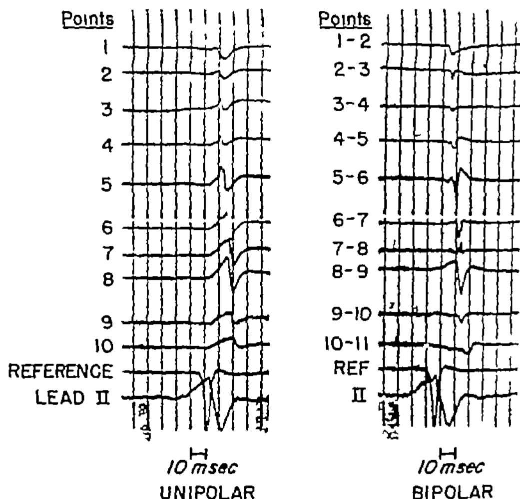


Fig. 7. Unipolar and bipolar tracings from an electrode insertion into the high right ventricular free wall in a dog with atrial septal defect. *Left* (*A*) The unipolar record shows a progressively more prominent upright deflection (approaching activity) from points 1 to 10 in an endocardial-to-epicardial direction. *Right* (*B*) The bipolar tracings show predominantly negative deflections indicating endocardial-to-epicardial spread of excitation. Points 1 and 2 were located adjacent to the subendocardium and points 9 to 11 were adjacent to the epicardium. Note that the deflections in the right ventricular free wall occurred during the terminal portion of the QRS complex of Lead II. See text for discussion.

the speed of endocardial spread is difficult to calculate with such electrodes however from the estimates of the isochronous planes intersecting the endocardium the values ranged from 2 0 to 6 0 (average 4 0) meters per second These values are in agreement with those of Draper and Weidmann[14] and Scher and associates[11] for normal dogs

II Necropsy findings In the control group no abnormalities were found The group with atrial septal defects revealed prominent dilatation of the right ventricle The crista supraventricularis appeared to be more prominent than normal Also the trabeculations of the right ventricular free wall appeared to be prominent in comparison to those in the normal group The thickness of the right ventricular free wall in normal animals varied from 3 to 5 mm and that in the dogs with atrial septal defects from 7 to 10 mm There was no significant difference between the two groups in the thickness of the mid left ventricular free wall (8 to 12 mm) Fig 8 *A* shows the usual type of atrial septal defect found the smallest defect measured 0 9 by 1 2 cm and the largest 1 2 by 1 5 cm The conduction system was demonstrated grossly by staining with Lugol s solution (Fig 8 *B* and *C*) The right bundle branch and the peripheral conduction system of the endocardium of the right ventricular free wall appeared to be normal [12] The high right septal surface and crista supraventricularis were almost devoid of conduction tissue

In summary a comparison of ventricular activation in the normal heart with that in the heart with an atrial septal defect revealed the following (a) Total ventricular activation time was increased from 33 to 36 msec (normal) to 43 to 46 msec (atrial septal defects) (b) During the first 15 msec the activation patterns were similar for both groups with double envelopment of the septum (c) There was a circular spread about both ventricular cavities with endocardial to epicardial spread of the activation wave front in the ventricular free wall in both groups (d) Activation of the crista supraventricularis in the normal dog occurred during the interval of 17 to 25 msec whereas in the dogs with an atrial septal defect this area was activated from 21 to 36 msec (e) Normally the latest areas of depolarization (29 35 msec) occurred in the upper middle portions of the interventricular septum in atrial septal defects the latest areas of activation (37-44 msec) occurred in the free wall of the high outflow tract of the right ventricle (f) The speed of electrical conduction through the muscle of the right ventricular free wall was similar for both groups of dogs i e 0 3 to 0 5 (average 0 4) meters per second

Discussion

The magnitude of the left to-right shunt in each of the dogs with an atrial septal defect was large comprising 65 to 81 per cent of the total pulmonary blood flow All of the group developed prolongation of the ventricular activation time from 33 36 msec to 43-46 msec and an increase in the spatial magnitude (average 0 44 to 1 17 mv) of the S portion of the QRS-E loop Additionally there was slowing of the vectorcardiographic tracing beginning with the inscription of the efferent limb of the S loop The S loop was displaced superiorly and posteriorly Quantitative analysis of the QRS-E loop preoperatively and postoperatively in the control group showed no significant changes which could be ascribed to the surgical procedure of the right thoracotomy and right atrial incision Therefore the QRS-E loop changes noted can be considered to have resulted from the left to right interatrial shunt

I Ventricular activation Studies in the normal control group of animals (Fig 3) revealed a sequence of activation which was consistent with the results of Scher and Young [18] In the group with atrial septal defect the pattern of ventricular excitation (Figs 5 and 6) was similar to that in the normal dogs during the first 25 msec During this period there was (1) no indication of delay or block of the right bundle branch and there was early activation of both the left and the right septal surfaces with double envelopment of the septum (2) the activation front encircled the subendocardial areas of both ventricular chambers and (3) the endocardial surface of the free wall of the high outflow tract of the right ventricle was

invaded. Invasion of the crista and free wall of the right ventricular outflow tract began 2 to 4 msec. later in the group with atrial septal defect. There was no evidence of conduction delay in the peripheral conduction system of the free wall of the right ventricle. In 2 dogs with atrial septal defects Purkinje potentials were recorded from the subendocardial area of the right ventricular free wall. No such potentials were recorded from the crista supraventricularis in either group.

The main differences in the pattern of activation were found after 25 msec. In the normal dog, the outflow tract of the right ventricular free wall and crista were

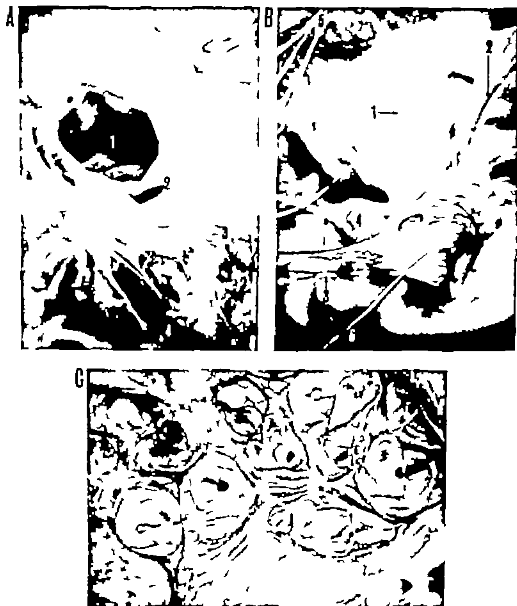


Fig. 8. A, Typical atrial septal defect found at necropsy. 1, Atrial defect. 2, Coronary sinus. 3, Tricuspid valve. B, Right bundle branch in a dog with atrial septal defect (iodine staining). The right bundle branch and its division were grossly normal. 1, Right bundle branch. 2, Superior division of right bundle. 3, False tendons of right bundle branch. 4, Papillary muscle of right ventricle. 5, Papillary muscle of conus. 6, Wires used to identify position of electrode insertion. C, Peripheral conduction system of right ventricular free wall in a dog with atrial septal defect (iodine staining). The arborizations of the peripheral conduction system appeared to be normal.

completely depolarized by 25 msec and final excitation from 25 to 35 msec occurred in the high basal portion of the ventricular septum and in a small area of the basal left ventricular free wall. In the group with atrial septal defect the period of 25 to 36 msec was occupied by depolarization of the crista with further invasion in the high right ventricular free wall while completion of activation occurred in the basal septum and left ventricle. The terminal portion of ventricular activation (36-44.5 msec) was completed as the wave front moved through the free wall of the basal portion of the outflow tract of the right ventricle. The speed of conduction through the muscle of the right ventricular free wall in normal dogs was similar to that in dogs with atrial septal defects, i.e., there was no interference with spread of the wave front in the free wall of the right ventricle in the presence of an atrial septal defect. Additionally, estimation of endocardial velocity indicated no interference with the spread of the impulse through the peripheral conduction system.

II. Correlation of ventricular activation with the vectorcardiogram. The ultimate value of the study of ventricular activation is in the providing of information in regard to the relationship between the curves recorded at a distance from the heart and the events within the heart. Sodi-Pallares and co-workers[17] in their studies of epicardial potentials found that the sequence of ventricular activation could be recognized by the vectorcardiographic curve if the electrical forces of one ventricle were markedly predominant. Additionally, they pointed out the complexities involved in such studies.

The canine heart presents an excellent preparation for the study of the relationship of the vectorcardiographic curve and the process of ventricular activation. Previous studies have shown the relationship of the anatomic orientation of the canine heart (Fig. 2 *C*) to the vectorcardiographic reference system. The two ventricles are situated vertically in a superior (right ventricle) and *inferior* (left ventricle) direction. The canine heart lacks much of the obliquity as related to the vectorcardiographic reference system that is inherent in the hearts of other mammals, e.g., human beings. A comparison of the sequence of ventricular activation with the vectorcardiographic curve is illustrated in Fig. 3 for the normal dog and in Figs. 5 and 6 for the dog with an atrial septal defect. Both the sequence of ventricular activation and the vectorcardiographic curves during the first 25 msec were similar in the normal and the atrial septal defect groups. However, during the period of 25 to 36 msec the spatial magnitude of the S loop was increased and displaced superiorly and posteriorly in the dog with an atrial septal defect as

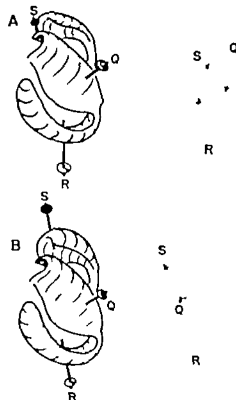


Fig. 9. Schematic representation of the major vectors of the QRS E loop as viewed from a right sagittal projection. *A*, Q, R, and S vectors of normal (preoperative) dog and the right sagittal QRS E loop. *B*, Q, R, and S vectors of dog with atrial septal defect and the right sagittal QRS E loop. Note the increased magnitude of the S loop which is displaced superiorly in the dog with atrial septal defect. Studies of activation showed that normally this portion of the QRS E loop was associated with excitation of the basal septum. In the case of atrial septal defects the hypertrophied crista supraventricularis and right ventricular free wall wave fronts contributed additional potentials to the S loop.

compared to that in the normal dog During this interval (25 36 msec) in the normal dog completion of activation occurred in the basal septum and left ventricle whereas in the dog with the atrial septal defect wave fronts in the crista supraventricularis and high right ventricular free wall contributed additional potentials not present normally These forces were displaced in a superior and slightly posterior direction in relationship to the central portion of the heart The normal dog had completed ventricular excitation and inscription of the vectorcardiographic curve by 36 msec In the dog with an atrial septal defect the additional period of 36 to 44 msec was occupied by completion of activation of the muscle of the free wall of the right ventricular outflow tract and was associated with the terminal inscription of the QRS&E loop Fig 9 presents a schematic representation of the orientation of the canine heart in the right sagittal view with the three major vectors (Q R and S) in the normal dog and in the dog with an atrial septal defect

These studies in animals provide information pertinent to present concepts of the genesis of the electrocardiographic changes in instances of atrial septal defects in man Becker and associates[19] have noted that experimental work in dogs can be interpreted in terms of human electrocardiography

As noted in dogs with atrial septal defects *there was no evidence of interference* with transmission of the electrical impulse through the right bundle branch peripheral conduction system or ventricular muscle Staining of the Purkinje fibers of the endocardium revealed grossly that the canine right bundle branch was normal as was also the peripheral conduction system of the right ventricular free wall (Fig 8 *B* and *C*)[11] This adds weight to the suggestion of Burch and De Pasquale[1] that re evaluation of rather arbitrary criteria for bundle branch block is needed

The crista supraventricularis was hypertrophied with associated increased thickness of the right ventricular free wall and dilatation of the right ventricular chamber Depolarization was occurring in these hypertrophied areas during an interval (25 35 msec) which normally was occupied only by activation of the basal septum Thus activation of both the crista and high right ventricular free wall contributed to the superior displacement of the S loop of the vectorcardiogram

The slightly later onset of depolarization (2 4 msec) of the high outflow tract of the right ventricle (Figs 5 and 6 plane I) as compared to normal can be explained by the greater distance traversed by the excitation process over the endocardium of the dilated chamber Neither this factor nor activation of the crista contributed significantly to the prolongation of the total depolarization process The greater thickness of the free wall of the outflow tract of the right ventricle undergoing activation at a normal rate required more time for completion of depolarization and resulted in prolongation of the total activation time

Summary

Vectorcardiographic and ventricular activation studies were conducted in dogs in which atrial septal defects had been produced surgically All animals developed large left to right shunts (65 to 81 per cent of total pulmonary blood flow) Quantitative vectorcardiographic analysis demonstrated no significant QRS&E loop changes in the control surgical group In dogs with atrial septal defects there was a twofold to threefold increase in the magnitude of the S loop which was displaced *superiorly*

A comparison of the patterns of ventricular activation in the normal dog and in the dog with an atrial septal defect revealed that (1) the total ventricular activation time increased in the group with the atrial septal defects (2) the pattern of activation was similar for both groups initially with double envelopment of the septum and invasion of the ventricular free walls (3) the later period of activation in the normal dog (25 35 msec) was attributed to excitation of the basal interventricular septum and left ventricle whereas during this time interval in the dogs with atrial septal defects excitation occurred in the high right ventricular free wall and crista supraventricularis in addition to the basal septum and (4) activation of the high right ventricular free wall occupied the

final period of excitation in the group with atrial septal defect and accounted for the prolongation of the total ventricular activation time

Hypertrophy of the right ventricular free wall accounted for the prolonged activation time with excitation occurring at a normal speed through the increased muscle mass There was no interference with the transmission of the electrical impulse through the right bundle branch peripheral conduction system or right ventricular muscle

Correlation of the sequence of ventricular activation with QRS$_s$E loop changes in the group with atrial septal defects showed that the excitation wave fronts of the crista supraventricularis and high right ventricular free wall accounted for the displacement of the S loop in a superior direction The terminal portion of the QRS$_s$E loop was attributed to completion of activation of the high right ventricular free wall

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Renal blood flow as influenced by changes in arterial, venous, and ureteral pressures

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Numerous studies have shown that renal blood flow remains relatively constant through a wide range of arterial pressure. The tendency for a relatively stable blood flow in spite of changes in perfusion pressure is an intrinsic property of the kidney. The term "autoregulation" has been employed to describe this phenomenon. Recent studies have accounted for autoregulation of renal blood flow on the basis of changes in extravascular pressure.[1-5] Experiments carried out in this laboratory[4, 6-11] have been concerned with autoregulation of flow in isolated kidneys. The present investigation is an extension of earlier studies designed to explore the possible intrinsic mechanisms operating within the intact kidney which account for autoregulation of blood flow. Results from the present work indicate a significant role of extravascular pressure in the renal autoregulatory phenomenon and contrast the hemodynamic effects of elevated renal artery, venous, and ureteral pressures.

Methods

Twenty-three intact (*in situ*) kidney preparations were employed as follows: adult dogs were anesthetized intravenously with sodium pentobarbital, 30 mg. per kilogram. The left kidney was exposed via an incision in the flank, with care being taken to avoid penetration of the peritoneal layer. The kidney was carefully freed from the peritoneal lining, and the artery, vein, and ureter were cleared of all extraneous tissues. No ligatures were placed in the region of the hilus in order to avoid obstruction of lymphatic vessels. Several blood vessels were ordinarily ligated in the anterior polar region of the capsule. The kidney was denervated surgically by section of nerve fibers and chemically by placing a gauze saturated with procaine around the renal pedicle. After heparinization of the dog (3 mg. per kilogram of body weight), the renal artery was temporarily ligated to permit cannulation of the renal vein with large bore polyethylene tubing. Renal vein outflow was collected in a plastic reservoir secured in a water bath, and blood was returned to the femoral vein of the dog by means of a Sigmamotor pump. Renal vein outflow was measured with cylinder and stop watch. Renal blood flows averaged 4.0 c.c. per minute per gram (range 2.3-5.5) at an average renal artery pressure of 122 mm. Hg (range 90-155). Large renal vein pres-

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sure deep vein pressure tissue pressure ureteral pressure and orifice renal artery pressure were measured via pressure transducers in a variety of experiments and registered on a Sanborn recorder as previously described [1 3 4 4 5]

Deep vein pressures in some intact kidneys were obtained as previously reported [6 9] The tip of a flexible polyethylene catheter was maneuvered deeply into the kidney substance at the level of the arcuate or interlobular veins and secured to prevent its dislodgment Criteria for successful placement of the tip of the catheter were (a) a marked increase in pressure when the tip of the catheter was advanced into veins deep within the renal substance (b) a rapid return in pressure after flushing of the catheter and (c) free withdrawal of blood through the catheter Technical errors inherent in the procedure have been described in two reports [9 12] Deep vein pressures were discounted if at termination of an experiment the tip of the venous catheter was observed not to penetrate beyond the margin of the pelvis Successful deep placement of the venous catheter was possible in approximately half of the total number of trials Large vein pressure was measured and maintained at zero millimeters of mercury In some experiments large vein pressure was increased in steps by adjustment of a screw clamp placed on the venous outflow catheter distal to the pressure measuring needle Ureteral pressure was increased in some experiments by occlusion of the ureteral catheter after its attachment to a pressure transducer

Previous reports have described the close agreement of needle pressure and deep vein pressure in the isolated kidney preparation [6] Renal blood flow has been reported to fall when resting tissue pressure and deep vein pressure were exceeded by experimentally elevated large vein or ureteral pressures [6 1] These previous findings resulted therefore in the establishment of four approaches to the approximation of tissue pressure in the kidney and these have been applied to the present study Tissue pressure was estimated by utilizing the following procedures (a) value of deep vein pressure (b) value of needle pressure (c) value of increased large vein pressure resulting in a detectable fall in renal blood flow and (d) value of increased ureteral pressure bringing about a detectable decrease in renal blood flow These values showed good agreement The average difference between the procedures in a given experiment was 2 mm Hg (range 0 5 mm Hg)

Systemic arterial pressure in some experiments was increased by transfusion or decreased by withdrawal of blood after transfusion Results were compared to those of experiments in which arterial pressure was increased by bilateral carotid artery occlusion as carried out by Thurau and Wober [13] The dog pump perfused kidney was utilized as an assay device to monitor levels of circulating constrictor agents after carotid artery occlusion

Table I Extravascular pressure and arterial pressure in the intact kidney (21 kidneys 21 dogs)

	Extravascular pressure (mm Hg)	*Mean arterial pressure (mm Hg)*	*Renal blood flow (cc /min /Gm)*
Mean	37	122	4 0
Range	18–50	90–145	2 3–5 5
S E	2	3	0 2

D t rm ned f om two [illegible] p [illegible] d [illegible] bed in t [illegible] 17 k d [illegible] D t [illegible] d by val [illegible] f deep [illegible] p [illegible] 4 kidneys

*Table II Deep vein pressure and renal artery pressure in intact kidneys**

Experiment number	*Deep vein pressure (mm Hg)*	*Renal artery pressure (mm Hg)*
13	45	123
14	37	145
15	37	128
16	61	151
17	45	131
18	24	110
19	50	140
20	41	109
21	41	128
Mean	42	129

* [illegible] recorded early [illegible] at time of equilibration of renal blood flow (A[illegible] renal blood flow = 4.2 cc/ [illegible] 2 7 5.5)

Table III Hemodynamic effects of elevation of large vein pressure in the intact kidney of 8 dogs (mean renal artery pressure 119 mm Hg)

Renal venous pressure range (mm Hg)	Control									
	0		1–15		16–30		31–45		46–60	
	R_T	RBF*	R_T	RBF	R_T	RBF	R_T	RBF	R_T	RBF
Mean	0 60	200	0 55	201	0 51	196	0 47	188	0 40	177
S E	0 05	17	0 05	16	0 05	11	0 04	14	0 04	14

*R_T Total resistance (RAP – LVP/F) (mm Hg/c /m) RBF = Renal blood flow (c /min)

Results

Experiments were carried out in intact dog kidneys to obtain estimations of extravascular pressure Table I provides average values of systemic arterial pressure (orifice renal artery pressure) and extravascular pressure in 21 intact kidney preparations Extravascular pressure values were estimated either by measurement of deep vein pressure (4 kidneys) or by values obtained from two to four of the independent procedures described above Pressures in 21 kidneys averaged 37 mm Hg (range 18 50) at an average orifice renal artery pressure of 122 mm Hg (range 90 145) Renal blood flows averaged 4 0 c c per minute per gram (range 2 3 5 5)

Deep vein pressures obtained as described previously were measured in 9 intact kidneys These data with simultaneously measured renal artery pressures are shown in Table II Deep vein pressure averaged 42 mm Hg in 9 kidneys with an average renal artery pressure of 129 mm Hg (mean renal blood flow 4 2 c c per minute per gram)

The effect of elevation of large vein pressure on renal hemodynamics is summarized in 17 intact kidney experiments (Table III) Large vein pressure was successively increased by adjustment of a screw clamp on the venous outflow catheter On the average renal blood flow is little influenced by increases in renal vein pressure (orifice vein pressure) through a wide range of venous pressure values Total resistance (RAP LVP/F) progressively decreases as a function of increased venous pressure varying from 0 to 60 mm Hg Renal artery pressures are maintained relatively constant in each experiment through the entire range of alteration in

Table IV Effect of increased large vein pressure on total and venous segment resistances in the

Experiment number	Large vein pressure											
	0				1 15				16–30			
	R_T†	R_T	DVP	RBF	R_T	R	DVP	RBF	R_T	R_T	DVP	RBF
13	1 1	0 4	48	104	1 0	0 3	50	106				
14	1 4	0 5	60	114					1 3	0 4	67	114
15	0 8	0	36	162	0 7	0 1	36	162	0 7	0 1	40	167
16	0 7	0 2	27	194	0 6	0 1	29	194	0 5	0 1	35	184
17	0 6	0 2	34	201	0 5	0 1	36	205	0 5	0 1	42	205

Renal artery pressure constant each experiment †R_T = Total renal resistance RAP – LVP F (mm Hg c/ml) R — Venous seg

venous pressure. In order to determine segmental resistances deep vein pressures were measured in 4 additional experiments in which large vein pressures were increased as in the previous table. Table IV demonstrates the effect of increased large vein pressure on total resistance (RAP-LVP/F) and venous segment resistance (DVP-LVP/F) in the intact kidney. Renal artery pressure is maintained relatively constant in each experiment. It is seen that renal blood flow remains relatively constant until large vein pressure approximates or exceeds resting deep vein pressure (extravascular pressure). Total resistance (R_T) decreases as a function of elevated large vein pressure (LVP) which is due in part to a decline in venous segment resistance (R_V).

The effect of elevation of ureteral pressure on renal blood flow in intact kidneys with and without a diuresis is illustrated in Table V. Control extravascular pressures obtained prior to elevation of ureteral pressures are shown in most experiments. Ureteral pressure was increased by occlusion of the ureteral catheter after attachment of the catheter to a pressure transducer. The occlusion period averaged 10 minutes (range 4-18). The average renal artery pressure at the time of ureteral occlusion was 129 mm. Hg (range 92-180). Results show that a decrease in renal blood flow ordinarily occurs when ureteral pressure approximates or exceeds resting extravascular pressure.

One aim of the present study was to increase renal artery pressure in order to assay the role of extravascular pressure in the regulation of renal blood flow. Systemic arterial pressures were increased in some intact kidney experiments by transfusion of blood or decreased after transfusion. The effect of the resulting change in renal artery pressure on extravascular pressure was determined. Extravascular pressure was estimated by the procedures described above. Table VI summarizes results from 7 kidney experiments and the arrows indicate the direction of change in pressure. Renal artery pressure was changed from an average of 101 to 155 mm. Hg, and autoregulation was observed in each instance. Approximately two thirds of the increase in total renal resistance (RSP/F) was accounted for by alterations in venous segment resistance (DVP-LVP/F). The difference in findings in regard to the magnitudes of extravascular pressure shown in Tables I and VI may be accounted for on the following basis: (a) a greater percentage of arterial pressures were below 100 mm. Hg in Table VI, in which range the extravascular pressures are ordinarily lower; (b) there is a tendency for extravascular pressure to be unstable and variable in the lower arterial pressure range[4, 6] and (c) unknown factors or influences may be elicited by removal of blood after transfusion (Table VI). It was difficult to achieve a steady state in the latter experiments but results compare favorably with those reported earlier in the perfused organ.[4] Other investigators[12] have achieved elevation of arterial pressure by carotid artery

*intact kidney**

range (mm. Hg)

31–45				*46–60*				*61–75*			
R_T	R_V	*DVP*	*RBF*	*R*	*R*	*DVP*	*RBF*	R_T	R_V	*DVP*	*RBF*
0.9	0.2	55	100	0.8	0.1	65	90				
1	0.3	65	110	1.1	0.2	78	108	1.0	0.2	85	98
0.6	0.1	56	148								
0.4	0.1	50	197								

...ment resistance: DVP-LVP/F (mm. Hg/cc./min.). DVP = Deep vein pressure (mm. Hg). RBF = Renal blood flow (cc./min.)

Table V Effect of increased ureteral pressure on renal blood flow in intact denervated kidneys

Experiment number	Without diuresis			With diuresis		
	Δ UP* (mm Hg)	Δ RBF (c c /min)	EP† (mm Hg)	Δ UP* (mm Hg)	Δ RBF (c c /min)	EP† (mm Hg)
1				0 → 71 → 73	168 → 180 → 122	
2				0 → 75	276 → 213	
3				0 → 85	183 → 150	48
4				0 → 85	120 → 94	48
5	0 → 65	156 → 130	44			
7	0 → 24	276 → 255				
8	0 → 44	167 → 156	45			
	0 → 63	188 → 167				
9	0 → 24 → 33	264 → 246 → 237	23			
11	0 → 53	140 → 150	48			
12	0 → 17 — 42	150 → 158 → 138	16			
13	0 → 25 — 68	110 → 114 → 92	38			
	0 → 93	137 → 120	85			
17	0 → 35 — 59	216 → 228 → 198	38			
22	0 → 72	207 → 278		0 → 95	258 → 180	
23	0 → 31	144 → 141	25			

I termed at values f U P (et l pressure) ar t be associated w th termed at lues f RBF (enal blood flow)
†EP = Extra ar lar pre d t rmined by l e of deep ve p ure d/ l e of cre d le ge pressu ult g in gradica decrease l blood flow

*Table VI Autoregulation and extravascular pressure in intact kidneys**

Experiment number	Δ Renal artery pressure (mm H)	Δ Extravascular pressure (mm Hg)	Δ Resistance		Per cent Δ R_V of total R
			R_T†	R_V†	
7	82 → 142	10 → 27	0 53 → 0 79	0 07 → 0 15	31
8	100 ← 185	9 ← 58	0 58 ← 0 81	0 05 ← 0 25	87
9	97 → 132	23 → 46	0 35 → 0 41	0 09 → 0 15	100
13	125 → 166	38 → 60	1 14 → 1 44	0 35 → 0 52	57
14	98 ← 172	8 ← 38	0 74 ← 1 00	0 06 ← 0 22	61
16	128 ← 151	47 ← 61	0 91 ← 1 09	0 14 ← 0 44	56
21	80 ← 133	13 ← 44	0 45 ← 0 61	0 07 ← 0 70	81
Mean	101 → 155	21 → 48	0 67 → 0 88	0 15 → 0 28	
S E	7 8	6 5	0 12 0 13	0 05 0 06	

Arrows d cat d rect f d g pressure
†R = RAP/RBF R = DVP – LVP/RBF
Mean RBF = 4 9 c/min/Gm (range 2 7 – 6 8) at RAP f 123 143 mm Hg

occlusion Several experiments were carried out utilizing this latter procedure to determine whether extrarenal influences were present to interfere with renal autoregulation Table VII illustrates the results from these studies An isolated kidney from a donor dog was perfused under conditions of controlled blood pressure or flow from an intact dog by means of a Sigmamotor pump and Starling resistance The common carotid arteries of the dog were temporarily occluded and the vascular effects on the isolated kidney were measured Changes in resistance in the perfused kidney could only be due to changing concentrations of vasoactive

agents in the blood. Results from 8 experiments show that when bilateral carotid occlusion occurs constrictor agents are released into the blood which cause a marked rise in renal resistance. Conversely, when carotid occlusion is released, a marked drop in total resistance in the isolated perfused kidney occurs within 1 to 3 minutes. Because of the magnitude of the changes in resistance when compared to the corresponding alterations in systemic arterial pressure, autoregulation of a kidney may be grossly interfered with by the extrinsic humoral influences. In parallel experiments it was shown that intra-arterial injections of catecholamines in the intact kidney resulted in significant decreases in deep venous pressure (extravascular pressure). The effect, therefore, of carotid occlusion on the intact kidney is twofold: (a) vasoconstriction of the renal artery and (b) a tendency to reduction of extravascular pressure. These experiments demonstrate the significant role of extrarenal humoral influences on renal vascular resistance.

Discussion

Results from the present work on the intact denervated kidney are in agreement with previously reported studies on isolated perfused kidneys[4, 8, 11] in regard to the significant role of extravascular pressure in the autoregulatory phenomenon. Findings from four independent procedures in determining extravascular pressures show essential agreement. These procedures are values of (a) deep vein pressure (arcuate vein or deeper), (b) needle pressure, (c) increase in large vein pressure which results in a significant fall in renal blood flow, and (d) increase in ureteral pressure producing a drop in renal blood flow. These independent measurements appear to adequately substantiate measurements of needle pressure previously reported by this laboratory and by others.[14, 16] The findings suggest that if bleeding is produced by the tissue pressure needle, it is venous in origin. Since deep vein transmural pressures approximate zero millimeters of mercury,[4, 9, 16] deep vein pressures are reflections of tissue pressure. A penetrating needle may puncture veins because of the large volume occupied by the venous segment.[17, 18] Extravascular pressures obtained in the present study are similar in magnitude to, although slightly higher than, those previously reported in isolated perfused kidneys.

A tendency to maintain a constant blood flow (autoregulation) was observed in the present study when both renal arterial and renal venous pressures were altered. The autoregulation observed when arterial pressure was increased was found to be produced in large measure by changes in extravascular pressure. The autoregulation observed with elevated renal venous pressures was partially accounted for on the basis of high resting extravascular pressures.

It has been shown[19] that capillary and tubular pressures are uninfluenced by changes in renal artery pressure. These results may be accounted for by release of catecholamine-like agents after carotid artery occlusion, as demonstrated in the

Table VII. Effect of carotid artery occlusion on vascular resistance of isolated perfused kidney

	Δ Systemic arterial pressure (mm. Hg)	Δ Renal resistance (mm. Hg/ /m)
Carotid occlusion (8 experiments)		
Mean	132 → 193	1 8 → 2 4
S.E.	3 9 12 5	0 2 0 4
Release of carotid occlusion (6 experiments)		
Mean	171 → 1 5	1 9 → 1 6
S.E.	7 9 5 ?	0 2 0 3

Arterial pressure or renal blood flow of isolated kid[illegible]

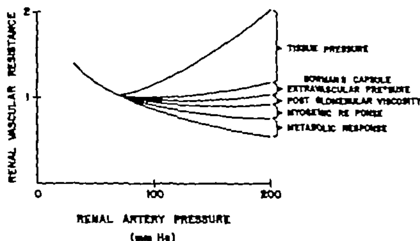


Fig. 1. Mechanism of autoregulation: suggested components of resistance (qualitative relationships based on results from past studies in this laboratory).

present study. Release of constrictor agents into the blood as a result of carotid occlusion would produce an exaggerated degree of autoregulation by arterial vasoconstriction, and a rise in extravascular pressure would not occur.

Values of directly measured deep vein pressures in the present study are corroborated by the other previously described procedures.[1,2,4,6,8,11] Additional information in support of the validity of this measurement is as follows: (a) obstruction of the venous bed by the catheter is unlikely because of the massive degree of collateralization;[17,19] (b) the size of the catheter does not influence the magnitude of the pressure;[1] and (c) the greater the degree of autoregulation when either arterial or venous pressure are increased, the higher is the recorded value of deep vein pressure.[8,11]

Obstruction of lymphatic vessels would not appear to influence the values of extravascular pressure obtained in the present study, since lymphatic vessels were not ligated. The finding that lymphatic outflow varies less when arterial pressure is increased than during elevation of venous pressure[9,1] is consistent with previously reported investigations;[1,2,4,6,8,11] increasing arterial pressure produces an elevated extravascular pressure which compresses lymphatic vessels. Therefore, lymphatic flow autoregulates.[1,26] Lymphatic pressure should not be taken as a measure of tissue pressure[22] unless the tip of the measuring catheter is in the renal parenchyma.[9] This relationship also exists between large vein and deep (arcuate interlobular) vein pressures.[8,11] It is difficult to interpret the significance of changes in lymphatic pressures and flows for the following reasons: lymph vessels of capsule and parenchyma anastomose;[3] acute lymphatic congestion has no effect on glomerular filtration rate and renal blood flow;[26] injections of epinephrine result in a decrease in the flow of urine but an increase in the flow of lymph.[3]

There has been much interest in the effect of increased ureteral pressure on renal hemodynamics.[4,12,3,4] Results from the present study are in agreement with those reported by Kiil and Aukland[28] and Winton.[13] Renal blood flow falls when ureteral pressure rises to values approximating or exceeding resting (control) extravascular pressure. In several experiments renal blood flow significantly increased after ureteral occlusion. This has also been reported by others,[28,29] and, on the basis of the data of the present study, initially occurs when ureteral pressure is well below the level of control extravascular pressure.

Fig. 1 is a schema of the proposed mechanisms operating to produce renal autoregulation. The several suggested components of resistance are depicted in a qualitative fashion. Tissue pressure is seen to account for most of the total change in resistance. Other components are Bow-

man s capsule extravascular pressure[4] changes in post glomerular viscosity[4,5] the myogenic response[11,12,17] and metabolic factors[22]

Summary

The mechanism of renal autoregulation is unclear The subject of the present investigation was the mechanism of autoregulation of blood flow in the intact (in situ) kidney The left kidney of the anesthetized dog was exposed via a flank approach Renal venous outflow was measured during control periods and after separate elevations of renal artery pressure renal vein pressure and ureteral pressure Extravascular pressure was estimated by obtaining values of (a) deep vein pressure (b) needle pressure and (c) elevations in large vein pressure and ureteral pressure resulting in significant decreases in renal blood flow Increases in renal artery pressure result in elevations of extravascular pressure which compress the renal vasculature Increases in renal vein and ureteral pressures do not decrease renal blood flow until approximating or exceeding resting tissue pressure Results from experiments with carotid artery occlusion indicate that extrarenal humoral influences may be superimposed on the autoregulatory phenomenon

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Re-excitation of the atrium "The echo phenomenon"

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In 1913 Mines reported an unusual arrhythmia in which an impulse originating from the atrium was conducted to the ventricle and then back into the atrium The counterpart of this arrhythmia that is beats of ventricular origin which were conducted to the atrium and then back to the ventricle was subsequently described by Moe and associates and by Rosenblueth[2] This type of disturbance has been termed *reciprocal beating*[1] or *echo responses* [3] and refers to the observation that an impulse initiated in one chamber of the heart may return to its chamber of origin causing a coupled extrasystole Two possible explanations have been offered for the above mentioned phenomena The first is that there are functionally separate pathways for atrioventricular transmission According to this view activity may enter one path in traveling from atrium to ventricle and then return in a retrograde direction over the alternate path to re-excite the atrium The reverse of this mechanism has been proposed for ventricular echo responses Moe and his co-workers have presented physiologic evidence for a dual A V transmission system and James[7] has recently published microscopic evidence of potential alternate pathways

A second explanation for reciprocal beats is re-entry According to this hypothesis an impulse can enter a region of slow conduction such as the A V node where the excitatory state may extend beyond the effective refractory period of adjacent fibers and re-enter the atrium causing an extrasystole A similar mechanism has been invoked to explain coupled extrasystoles within the sinoatrial node[8] as well as atrial and ventricular echo responses

In recent experiments designed to study pacemaker activity during vagal escape[9] we frequently observed reciprocal atrial beats and other atrial arrhythmias Electrical activity was recorded from selected portions of the specialized conduction system and these records provide certain additional information concerning reciprocal responses and the concept of a dual A V transmission system

Methods

Experiments were performed on 10 mongrel dogs which weighed between 16 and 22 kilograms Anesthesia was induced with pentobarbital sodium (25 mg per kilogram) and ventilation was controlled with a Jefferson pump

A right thoracotomy was performed through the fourth intercostal space the right atrium was opened under temporary inflow occlusion and a bipolar recording electrode was implanted over the bundle of His (Fig 1) A second bipolar recording electrode was implanted on the epicardial

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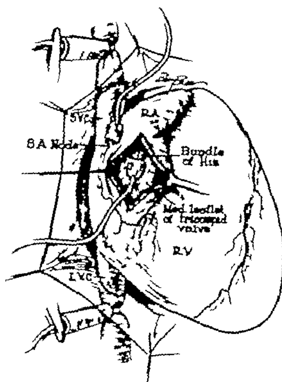


Fig 1 Preparation Recording electrodes placed over the bundle of His and the region of the sinoatrial (SA) node

surface of the right atrium in the region of the sinoatrial node Signals from each electrode were amplified with Tektronix 122 preamplifiers and displayed on a Tektronix 502 dual beam oscilloscope Frequencies below 80 c p s and above 1 000 c p s were filtered out to sharpen the desired signals Records were photographed with a DuMont 321 oscilloscope camera at a paper speed of 400 inches per minute

The distal end of a crushed or severed vagus nerve (right or left) was placed in a stimulating electrode and bathed in mineral oil Temperature in the neck was maintained with a heated collar The nerve was stimulated through an isolation unit using a Grass impulse generator Usual stimulation variables were 8 to 10 volt pulses of 5 msec duration at a frequency of 20 to 30 per second Signals from the two recording electrodes were photographed prior to and during approximately 30 seconds of vagal stimulation

Results

Reciprocal atrial beats were observed in all animals during vagal stimulation In Fig 2 examples of atrial re-excitation are shown Electrical activity was recorded from the region of the sinoatrial node (*SA*) the atrial septum (*A*) the bundle of His (*H*) and the basal interventricular septum (*S*) Panel A is the control record prior to vagal stimulation In Panels B and C during vagal stimulation the A V nodal delay was increased (lengthened A H interval) and after ventricular activation atrial re excitation occurred In contrast to the primary atrial beats the sequence of atrial activation was reversed during re-excitation that is the atrial septum preceded the sinoatrial node

Fig 3 illustrates tracings from an experiment in which atrial re excitation was observed to follow conducted beats as well as in the presence of complete A V block Panel B shows an idioventricular beat with retrograde conduction into the atrium In Panel C a normally conducted beat was followed by atrial re excitation The sequence of atrial activation during the re-excitation beat was identical to that shown in Panel B during retrograde conduction into the atrium Panel D shows retrograde re excitation in the presence of complete heart block The primary atrial beat was blocked at a point proximal to the His electrode (presumably the A V node) and was followed by retrograde atrial re-excitation

The records shown in Fig 4 illustrate a similar type of atrial re-excitation after beats in which the pacemaker was in the ventricle In Panel B a slow idioventricular rhythm was present and activity was conducted retrograde into the atrium In Panel C atrial activation was followed by re-excitation of the atrium again in a retrograde sequence

Fig 5 illustrates a different type of atrial re-excitation In Panel B during vagal stimulation the atrial rate was slow and A V transmission was blocked In Panel C an atrial extrasystole was coupled to the regularly occurring atrial beats In both the primary atrial response and the extrasystole the sinoatrial node preceded the atrial septum and the complexes were of similar contour In this form of atrial re-excitation there was little or no change in the sequence of atrial activation from that observed during the normal beat

Fig 6 shows that both types of atrial re excitation can occur in the same animal and when they occur together result in repetitive atrial extrasystoles In Panels B and C re excitation beats occurred which were similar to the primary atrial responses In Panel D early atrial re excitation was followed by a second re excitation beat in which a retrograde sequence of atrial activation was present

Atrial fibrillation was observed in 7 of 10 animals during vagal stimulation Records from 2 such experiments are shown in Fig 7 In the upper tracings two control beats are shown in Panel A In Panel B during vagal stimulation an idioventricular beat with retrograde conduction into the atrium was followed by atrial re excitation and by a regular tachycardia which subsequently degenerated into atrial fibrillation (Panel C) In the lower tracings Panel A again shows the control rhythm prior to vagal stimulation In Panel B during vagal induced complete A V block the first atrial beat was followed by a reciprocal atrial response and then by a regular atrial tachycardia which rapidly degenerated into fibrillation (Panel C) All instances of atrial fibrillation were preceded by early reciprocal atrial responses

Discussion

The records shown in Figs 2 and 3 illustrate one type of atrial re excitation In these responses the sequence of activation of the sinoatrial node and atrial septum was the reverse of that observed during beats originating from the sinus node The pattern of atrial activation during this type of re excitation was similar to that which occurred when beats of idioventricular origin were conducted in a retrograde manner into the atrium (Fig 3) If it is assumed that the pathway for atrial activation which followed idioventricular beats involved retrograde conduction over the bundle of His and the A V node then the data suggest that re-excitation beats entered the atrium over a similar pathway The finding of identical atrial re-excitation in the absence of recorded activity from the bundle of His (Fig 3) indicates that the pathways involved did not extend below the A V node It is possible that atrial re excitation resulted from an ecto

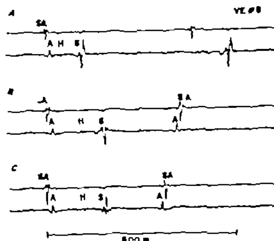


Fig 2 Atrial re-excitation Panel A Control Panels B and C During vagal stimulation SA Sinoatrial node A Atrial septum H Bundle of His S Interventricular septum In Panels B and C conducted beats are followed by retrograde atrial re-excitation (Retouched)

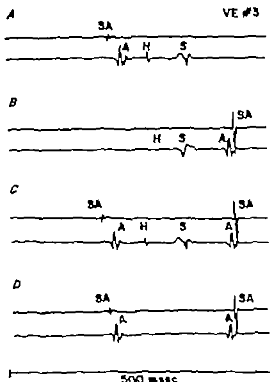


Fig 3 Atrial re-excitation Panel A Control Panels B C and D During vagal stimulation SA Sinoatrial node A Atrial septum H Bundle of His S Interventricular septum Panel B shows retrograde atrial activation after a ventricular escape beat Panel C shows a reciprocal response identical to retrograde activation in Panel B Panel D shows a reciprocal response in the presence of complete block (Retouched)

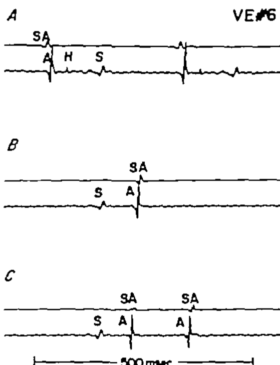


Fig. 4. Atrial re-excitation. *Panel A*, Control. *Panels B* and *C*, During vagal stimulation. *S1*, Sinoatrial node. *A*, Atrial septum. *H*, Bundle of His. *S*, Interventricular septum. Panel *B* shows a ventricular escape beat with retrograde atrial activation. Panel *C* shows a ventricular escape beat with retrograde atrial activation followed by retrograde atrial re-excitation. (Retouched.)

atrial pacemaker. This seems unlikely, however, for three reasons. First, re-excitation beats were observed only during vagal stimulation, a physiologic intervention which suppresses all known supraventricular pacemaker tissue. Furthermore, during re-excitation responses the sequence of atrial activation was the same as during responses propagated from the ventricle (Fig. 3). Thirdly, the reversed sequence of atrial activation was observed in these experiments only in atrial responses coupled to primary atrial beats. A dominant pacemaker in the region of the atrial septum was not observed in any of the tracings. For the reasons noted above, it is suggested that the impulse re-entered the atrium from the A-V node and not from an ectopic supranodal site.

These data support the view that reciprocal atrial beats result from retrograde re-excitation and that the stimulus producing the extrasystole originates from the region of the A-V node. The observations are consonant with both the re-entry and dual pathway hypotheses. However, if a dual A-V conduction system accounts for the observed phenomena, the communication between the two paths appears to be located proximal to the His electrode and therefore presumably within the A-V node.

James[7] has recently published a detailed morphologic study of the human atrioventricular node. He demonstrated at least three separate bundles of specialized atrial fibers which enter the A-V node at different levels, as well as a "bypass tract" which circumvents the A-V node and leads directly into the bundle of His. The groups of fibers which join the A-V node in its mid-portion provide a structural basis for potential pathways over which atrial re-excitation might occur. The data presented in this report would be consistent with such a mechanism. The observation that reciprocal beats can occur in the presence of complete heart block and in the absence of recorded activity from the bundle of His would appear to indicate that the "bypass tract" was not utilized.

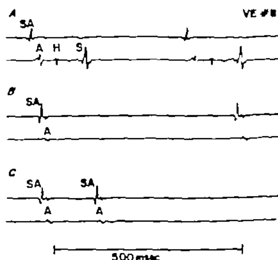


Fig. 5. Atrial re-excitation. *Panel A*, Control. *Panels B* and *C*, During vagal stimulation. *S1*, Sinoatrial node. *A*, Atrial septum. *H*, Bundle of His. *S*, Interventricular septum. Panel *B* shows a low atrial rhythm with complete A-V block. Panel *C* shows a coupled atrial premature systole (re-excitation) in which the sequence of activation is identical to the beat originating from the S1 node region in Panel *B*. (Retouched.)

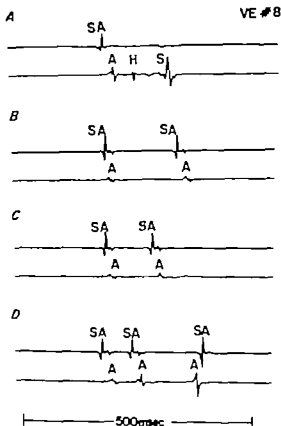


Fig 6 Recurrent atrial re-excitation *Panel* A Control *Panels B C* and *D* During vagal stimulation *SA* Sinoatrial node A Atrial septum *H* Bundle of His *S* Interventricular septum Panel *B* and *C* show coupled atrial premature systoles which appear to originate from the region of the *SA* node I Panel *D* an early coupled premature systole from the *SA* node followed by a reciprocal atrial response (Retouched)

The records shown in Fig 5 illustrate a second type of atrial re-excitation in which the sequence of activation at the sinoatrial node and atrial septum was the same during re-excitation as that observed during beats initiated from the sinus node This finding suggests that the origin of the normal beat and of the re-excitation response was the region of the sinoatrial node Hoffman and Cranefield have proposed that this type of coupled atrial extrasystole results from re-entry They postulated that an impulse initiated in one region of the sinoatrial node might propagate rapidly through atrial muscle to a different area of the sinoatrial node enter the node where it would propagate at a slow rate and then re-enter the atrium at the end of the atrial refractory period Re-excitation of this type would be expected to produce a normal pattern of atrial activation

In Fig 6 the primary atrial response was followed by a premature systole which appeared to result from re-entry within the sinoatrial node (Panels B and C) In Panel D a very early premature atrial systole was followed by a reciprocal atrial response This sequence of events an early premature beat followed by a reciprocal response is similar to the phenomena reported by Moe and associates and labeled *atrial echoes* In Moe's experiments the echo responses were elicited by an externally induced premature atrial beat Although the echoes described by Moe

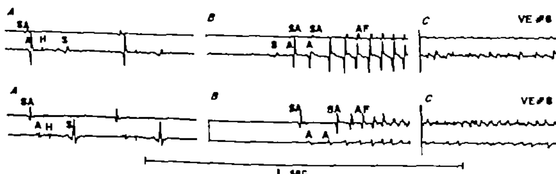


Fig 7 Atrial fibrillation *Upper tracings* Panel *A* Control *P* B and C During vagal stimulation *SA* Sinoatrial node A Atrial septum *H* Bundle of His S Interventricular septum In Panel B a ventricular escape beat with retrograde atrial activation is followed by re-excitation a regular atrial tachycardia (*AF*) and atrial fibrillation (Panel *C*) *Lower tracings* *P* and Control *Panels B* and C During vagal stimulation Panel *B* the first atrial beat fails to conduct to the ventricle but is followed by a reciprocal response by an atrial tachycardia (*AF*) and by atrial fibrillation (Panel *C*) (Retouched)

occurred somewhat later than those presented in this report this could be accounted for by the effect of vagal stimulation on reducing the atrial refractory period

Many investigators have analyzed the mechanism of atrial fibrillation however the majority of studies have been concerned with factors which enable this arrhythmia to be self sustaining or self perpetuating Despite a number of experimental methods for producing atrial fibrillation there is little evidence available in regard to the event or events which initiate this arrhythmia in the intact animal or man It is generally agreed that atrial fibrillation can be started by a stimulus delivered to the atrium when cells are in varying states of recovery of excitability[10,11] Moe has recently proposed that a wave front entering an irregularly excitable atrium is slowed or divided at refractory areas and thereby degenerates into multiple wavelets which lead to atrial fibrillation[12] According to this hypothesis the basic condition which must exist in the atrium is nonuniform excitability enhanced vagal nerve activity produces such a state of nonuniform excitability in the atrium[13] When this condition exists an impulse propagated into the atrium may initiate fibrillation The findings presented in this report demonstrate that atrial re-excitation is a common event during vagal stimulation In addition under the conditions of these experiments atrial fibrillation was uniformly preceded by re-excitation These observations suggest that reciprocal beats may represent an intrinsic mechanism which can provide the fibrillatory stimulus

Summary

During vagal stimulation in dogs reciprocal atrial beats or echoes were observed repeatedly Records of electrical activity from the sinoatrial node the atrial septum and the bundle of His demonstrated that echo responses were characterized by retrograde atrial activation and appeared to originate from the region of the A V node The observation that echo responses can occur in the presence of complete A V block indicates that the pathways involved do not extend below the A V node A second type of atrial re excitation was also observed which appeared to originate from the region of the sinoatrial node and was characterized by a normal sequence of atrial activation Atrial fibrillation occurred in 7 animals during vagal stimulation and in each instance was preceded by a reciprocal response This suggests that under certain conditions a reciprocal response may initiate atrial fibrillation

The valuable advice of Dr Stanley J Sarnoff and the technical contributions of Mr Frank Perry and Mrs Carrie Scott are gratefully acknowledged

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The effects of quinidine on the metabolism of glucose-U C^{14} and palmitate-U C^{14} by heart muscle

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The depressive effects of quinidine on myocardial excitability are well known Several investigators have shown that quinidine in pharmacologic concentrations suppressed the oxygen consumption of myocardial tissue slices[1,2] The mechanism by which quinidine exerts this effect has not been clearly established

The purpose of this investigation was to study directly the effects of therapeutic and toxic concentrations of quinidine on the oxidation of glucose and free fatty acids the major substrates for the production of energy by heart muscle[3,4] Glycolysis was studied directly by measuring glycogen breakdown and net lactate formation

Methods

Well fed mongrel dogs which weighed between 10 and 12 kilograms were anesthetized by the intravenous injection of 30 mg per kilogram of sodium pentobarbital The hearts were quickly removed and placed in oxygenated chilled Krebs Ringer phosphate buffer Approximately 150 mg uniform 0 5 mm slices of left ventricle from 8 dogs were prepared with a Stadie Riggs slicer Four slices were utilized for each control and with each concentration of quinidine

Oxygen consumption was determined by the direct method of Warburg with 100 per cent oxygen as the gas phase at 37°C Krebs Ringer phosphate was the buffer medium The composition of the buffer medium was as follows 093M NaCl 048M KCl 00125M $CaCl_2$ 0012M $MgSO_4$ 033M sodium phosphate buffer of pH 7 4 Chromatographically pure glucose U C^{14} was obtained from New England Nuclear Corporation and U S P quinidine sulfate from Burroughs Wellcome & Company Each Warburg flask contained 2 85 c c of buffer medium containing 10 mM of glucose U C^{14} (specific activity 10 000 CPM/μM) The following final concentrations of quinidine sulfate were used 1×10 M 5×10^{-4}M and 1×10^{-3}M The manometers and flasks were gassed for 5 minutes with 100 per cent oxygen and stabilized for 10 minutes prior to the initial reading Oxygen consumption was determined at intervals of 30 minutes for a period of 2 hours

The uptake of glucose was determined from the difference between the initial and final concentration of glucose in the

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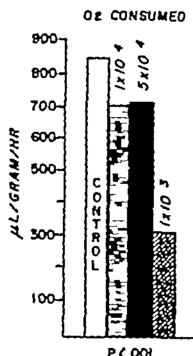


Fig. 1. Oxygen consumption was suppressed by both 1×10^{-4} and 5×10^{-4}M quinidine. 1×10^{-3} quinidine profoundly depressed oxygen consumption of the tissue slices.

buffer after precipitation of protein with 5 per cent perchloric acid. Glucose was measured by the Nelson-Somogyi method.[6] Glycogen content of tissue was determined by the method of Good, Kramer, and Somogyi.[7] Lactate was measured by the enzymatic method of Horn and Bruns.[8] $C^{14}O_2$ was trapped in CO_2-free NaOH in the center well of the Warburg apparatus and precipitated as $BaCO_3$. The washed $BaCO_3$ was planchetted and counted in a thin end-window gas-flow proportional counter. Corrections for self-absorption were made according to Karnofsky and associates.[9] The results were expressed as micromoles (μM) of glucose per gram of wet tissue per hour.

The oxidation of palmitate-1-C^{14} was estimated by using a specially designed metabolic flask for collecting $C^{14}O_2$.[10] Palmitate-1-C^{14} 0.125 mM (specific activity 1.25 μC/μMole) was added to Krebs-Ringer bicarbonate buffer (Umbreit) with the above-mentioned concentrations of quinidine. The flasks were sealed with rubber stoppers and gassed with 95 per cent oxygen and 5 per cent CO_2. The tissue slices were incubated for 2 hours at 37°C in a Dubnoff metabolic shaker. The reaction was terminated by the addition of 0.3 ml. of 6N H_2SO_4 and 0.3 ml. of 1M hyamine hydroxide was added to a suspended Pyrex glass center well to trap all $C^{14}O_2$. The flasks were shaken for 2 hours after the addition of the acid in order to insure complete recovery of $C^{14}O_2$. The spontaneous decarboxylation of palmitate-1-C^{14} was determined for each experiment. The Pyrex center well was transferred directly into a counting vial containing 10 ml. of toluene scintillation containing 7.2 Gm. per liter of 2,5-diphenyloxazole and 0.18 Gm. per liter of 1,4-bis-2-(4-methyl-5-phenyloxazolyl)-benzene and counted in a liquid scintillation spectrometer. The results were expressed as counts per minute per gram wet weight of tissue. Statistical comparisons were computed using analysis of variance.[11] P values computed by the t test are indicated under each figure.

Results

Oxygen consumption. There was an equal suppression ($p < 0.001$) of oxygen consumption by both 1 and 5×10^{-4}M quinidine. Quinidine in a concentration of 1×10^{-3}M caused a marked suppression of oxygen consumption (Fig. 1).

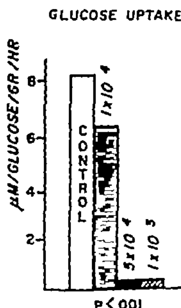


Fig. 2. Effect of quinidine on the uptake of glucose.

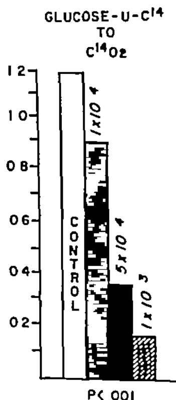


Fig. 3. Effect of quinidine on the oxidation of 10 mM of glucose U C

Glucose uptake. The uptake of glucose was reduced ($p < 0.001$) with quinidine in a concentration of 1 X 10-4M. Quinidine in concentrations of 5 X 10-4 and 1 X 10-3M produced almost complete inhibition of the uptake of glucose by the tissue slices (Fig. 2).

Glucose oxidation. There was a 25 per cent suppression of the oxidation of glucose to $C^{14}O_2$ in the presence of 1 X 10-4M quinidine ($p < 0.001$). A greater inhibition was noted with higher concentrations of quinidine (Fig. 3).

Glycogen content. The direct effect of quinidine on glycolysis was measured by determining the glycogen content of myocardial tissue slices at the end of the 15 minute period of gassing prior to measurements of the uptake of oxygen (time zero or T_0) and after 2 hours of incubation with increasing concentrations of quinidine. Since cardiac glycogen is higher in the fasted state[1] slices from the hearts of dogs which had fasted for 24 hours were used. Net glycogen breakdown in the slices incubated with 1 X 10-4M quinidine was not significantly different than in the control (Fig. 5). With increasing concentrations of quinidine glycogen breakdown was accelerated.

Net lactate formation. The lactate formed was not different between the control group and slices incubated with 1 X 10-4M quinidine (Fig. 4). With higher concentrations of quinidine net lactate formation was increased ($p < 0.001$).

Palmitate-U-C14 oxidation. There was a 60 per cent inhibition of the oxidation of palmitate-U-C14, a major substrate for myocardial metabolism, by 1 X 10-4M quinidine (Fig. 6). There was further suppression of oxidation of palmitate by 5 X 10-4M quinidine and complete inhibition by 1 X 10-3M.

Discussion

Pharmacologic concentrations of quinidine have been shown previously to suppress oxygen consumption of heart slices.[1] Webb, Saunders and Nakamura first studied the depressant effect of quinidine on the oxygen consumption of rat myocardial tissue slices and indirectly studied its effects upon glycolysis. From these indirect observations they concluded that the primary site of the metabolic effects

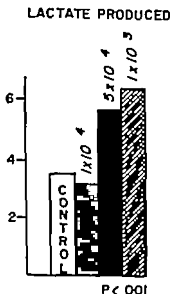


Fig. 4. Effect of quinidine on the net production of lactate

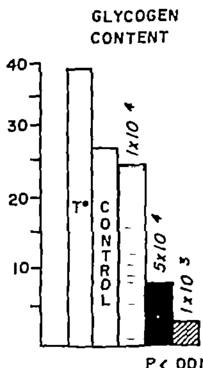


Fig. 5. Effect of quinidine on glycogen content of heart slices from dogs fasted for 24 hours.

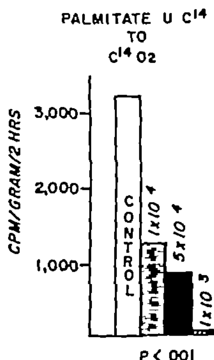


Fig. 6. Effect of quinidine on oxidation of palmitate-U C^{14}.

of quinidine was upon the glycolytic pathway. Uyeki, Geiling, and DuBois[1] subsequently studied the respiration of heart slices in the presence of various substrates by the conventional Warburg manometric technique and confirmed a marked suppression of oxygen consumption by 1×10^{-4}M quinidine. However, they were unable to demonstrate any appreciable inhibition of glycolysis by even higher concentrations of quinidine.

This suppression of oxygen consumption by 1×10^{-4}M quinidine, a nontoxic concentration which has been shown to increase the refractory period and depress the mechanical activities of heart muscle, is accompanied by a decrease in the uptake of glucose and a 25 per cent inhibition of the oxidation of glucose. There was a 60 per cent inhibition of the oxidation of palmitate U C^{14} by this concentration of quinidine. Glycolysis (breakdown of glycogen and increased formation of lactate) was not affected.

Higher and presumably toxic concentrations of quinidine markedly inhibited the uptake of glucose and the oxidation of both glucose and palmitic acid. Glycolysis was sharply accelerated, as indicated by an increase in glycogen breakdown and net lactate formation.

The conclusion is that quinidine suppresses myocardial oxygen consumption by inhibiting the oxidative pathways for the major cardiac substrates, glucose and free fatty acid. This suppression of oxidative metabolism of heart muscle by quinidine may be an important factor in its therapeutic and toxic effects on the myocardium.

Summary

Quinidine sulfate in low concentrations suppressed the oxygen consumption of myocardial tissue slices by inhibiting the oxidative pathways for the metabolism of glucose and free fatty acid. Anaerobic glycolysis, measured directly, was unaffected. Higher and presumably toxic concentrations of quinidine sharply inhibited the oxidation of glucose and free fatty acids and accelerated the breakdown of glycogen.

This profound effect of quinidine on oxidative myocardial metabolism may be

an important factor in depressing myo cardial excitability and contractility

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A diaphragm isolator and spring-driven dye injector for efficient multiple determinations of cardiac output by indicator dilution

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A Diaphragm isolator for withdrawal of blood

When one is making repeated indicator dilution determinations of cardiac output it is usually necessary to return the blood especially if the patient is a small child. Because of the tendency of blood to jam glass syringes the diaphragm isolator described in Fig. 1 was developed. The use of Plexiglas and silicone rubber has made the unit easy to clean and sterilize. The units have increased the efficiency of the procedure during many hundreds of determinations in a pediatric cardiology laboratory† and in experimental work with dogs over the last 3 years. If autoclaving instead of cold sterilization is desired the front chamber could be made of Teflon.

By using a conical front section the diaphragm makes contact at the outermost rim of the chamber first when discharging blood. Then as the diaphragm is driven forward by fluid from the drive syringe the blood is effectively squeezed out leaving much less than 1 ml of blood in the chamber. The groove (*B*) is necessary *so that the tubing and cuvette can* be flushed with about 5 ml of saline. If all air bubbles are removed from both the blood and water sides of the diaphragm the system will be noncompressible and thus the rate of withdrawal will be as accurate as that of the original withdrawal system. The unit as described will accommodate about 35 ml of blood. A unit with a conical chamber 0 75 inch deep and 3 5 inches in diameter with a 23 degree angle will *hold* about *75 ml*. At current medical school shop rates construction cost is about $35.

B Spring driven dye injector

For repeated determinations of cardiac output multiple injections of the same amount of dye are required. If high reproducibility in volume of dye injected is attained and the same arrangement is used for calibration as for determinations the requirement of accuracy of measurement of the injected volume or concentration can be eliminated for the actual amount of dye injected is cancelled in subsequent calculations. The syringe injector described (Fig 2) has permitted serial determinations at intervals of less *than 1 minute in children* and eliminates the necessity for weighing dye syringes

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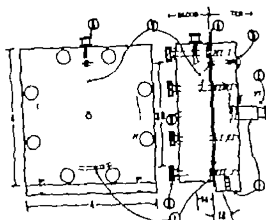


Fig 1 Diaphragm isolator *A* Silicone rubber diaphragm (1/32 inch) (Rostbor Resin Corporation Little Falls N J) This can be autoclaved is non toxic and is highly inert to cleaning agents *B* Round bottomed (1/16 inch ball-end mill) channel 1/16 inch deep permits flushing the line and cuvette with sterile saline when the diaphragm is pressed against the front of the chamber at the end of a run (The front chamber and this groove must be highly polished for easy cleaning) *C* Male Luer Lok connection with Teflon washer as gasket for connecting syringe for flushing *D* Screw (6-32) with Teflon gasket to permit easy removal of bubbles when rear chamber is being filled with water *E* Male Luer Lok fitting for easy connection to a constant rate withdrawal syringe *F* Front piece is relieved 0 010 to 0 020 inch leaving a ½ inch wide rim so that pressure from the clamping screws is concentrated in a small area to provide an excellent gasket *G* Clamping screws 10 3? knurled thumb screws need to be only moderately tight for perfect seal if ⅛ inch rim (*F*) is used *H* Tapered hole for Clay Adams PE 320 polyethylene tubing with 0 015 inch taper in ½ inch using No 29 30 and 31 twist drill or a special reamer This fitting withstands several thousand millimeters of mercury of pressure and has not come loose during use No metal or crevices which are difficult to see or clean are present with this design A male Luer Lok fitting such as used on the Gilford cuvette may be screwed in here A ¼ inch thick piece would then be adequate *I* Support either by clamping on the 1/16 inch round piece in the center of the isolator or by screwing the rear piece to base plate

or flushing dye injection lines It has been used with hundreds of determinations of cardiac output in dogs A three way stop cock is mounted on the Luer Lok connection at the end of the dye injector so that a 20 ml syringe can be used as a reservoir for the dye The dye mixed in the vial supplied by the manufacturer is then aspirated into this syringe The 1 ml syringe is repeatedly filled and emptied from the 20 ml reservoir in order to assure uniform mixing and eliminate bubbles in the dye injector Two injections of 0 5 ml each are diluted to 5 00 ml with saline

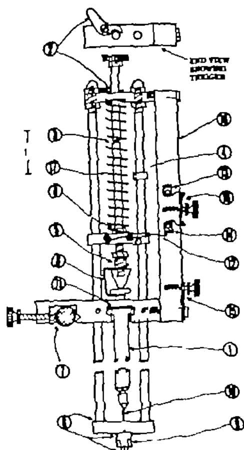


Fig 2 Dye injector *1* Tuberculin syringe glass 1 ml with plunger about 0 18 inch in diameter *2* Trigger which engages slot (3) when syringe is filled to 0 50 ml *3* Square-shouldered groove *4* A stop slightly beyond filled level for alignment for easy engagement of trigger *5* Adjusting nut with lock nut for adjustment to ± 0 001 ml *6* Rust guarding spring for syringe plunger *7* Support stand *8* Soldered joints *9* Male Luer Lok taken from a discarded syringe *10* Hypodermic needle 17 Gm to provide flexibility for slight lateral misalignment *11* Silicone rubber washer to provide constant pressure on syringe against needle but to permit differences in expansion during washing and sterilizing *12* Piano wire spring contact for event marking *13* Contact about / inch in front of filled position to indicate start of injection *14* Contact just before empty position to indicate end of injection *15* Ground connection for event marker *16* Connection to event marker of recorder *17* Piano wire (0 041 inch) spring with about 1 600 grams of force in the full and 600 gram in the empty position *18* Plexiglas bar to insulate contacts (Teflon if the unit is to be autoclaved)

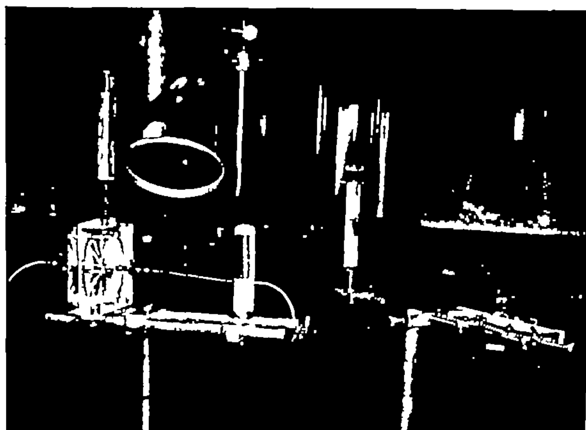


Fig 3 Arrangement of diaphragm isolator and spring driven dye injector

for preparation of standards The system is connected to a length of about 100 cm of polyethylene tubing (I D of 0 58) This highly flexible tubing usually placed coaxially in a larger but shorter piece of tubing for increased rigidity is advanced through a femoral vein to the region of the right atrium One 0 5 ml injection is used to fill and flush the dye catheter

When a determination is desired the unit is triggered placing an event mark on the record and injecting the dye in 0 2 to 0 3 second The fine bore catheter is necessary to prevent breakage of the syringe by the spring Flushing is not required because the volume of the catheter which might have dye washed out between determinations is only about 2 6 µl per centimeter of catheter Even 1 cm of washout by pulsatile pressures in the body represents only 0 5 per cent of the total injection Calibration is accomplished by ejecting water into a 10 ml beaker and immediately weighing on an automatic analytical balance The volume of injection of the injector presently in use is 0 5060 ± 0 0004 S D ml Thus the coefficient of variation is 0 08 per cent Although long term stability between uses of the injector is not required when assembled about a year before the calibration was 0 505 ml

Current injectors under construction will be modified by placing a slot in the support bar which bears against the barrel so that a separately sterilized syringe can be easily inserted into the unit Construction cost is about $75

I wish to thank Mr John McCutchan Instrument Machinist Department of Physiology for his fine workmanship in building these devices for use here and elsewhere

Indicator-dilution techniques in the estimation of renal blood flow

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Observations of renal blood flow based upon clearance techniques depend for accuracy upon a relatively steady state. Alterations in flow may not be accurately reflected in determinations of clearance because of the delay in and the mixing during transport of the excreted substance. A tremendous mass of experimental work has codified the conditions under which accurate estimates of renal blood flow may be made from clearance values. The method is poor when rapid changes in renal blood flow are to be followed. A method of instantaneous measurement of renal blood flow would be useful directly or for calibration of a flowmeter. *It is the purpose of this investigation to describe a method approaching this using the principles of indicator dilution.*

Preliminary observations in the dog showed that indicator-dilution curves drawn from the iliac artery after injection into the left side of the heart yielded prominent recirculation curves with clearly exponential downslopes. These were shown to be present also in curves drawn from the inferior vena cava below the entrance of the hepatic veins. At this site, where the mixing volume of the lungs is excluded, recirculation curves have clearly exponential downslopes which may be easily extrapolated. It was suggested that these curves *represented early* recirculation through the kidneys. Curves withdrawn from a renal vein after injection into the thoracic aorta verified this hypothesis. A study was undertaken to determine the usefulness of such curves in estimating renal blood flow.

Theory

The indicator-dilution principle states that the amount of indicator moved through a flow system from point of injection to point of observation is the product of the flow, the concentration, and the time; thus

$$I = F \times C \times t \qquad (1)$$

where I is the amount injected, F is the flow, C is the concentration at the point of observation, and t is the time of the passage of I.

When the injection is instantaneous and the time-concentration curve is integrated, C × t becomes the area under the observed curve.

Thus

$$F = \frac{I}{C \times t}$$

or

$$F = \frac{I}{\text{area}} \qquad (2)$$

Now, in the case of the kidneys, we can determine the area of the curve at the

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entrance of the renal arteries. Thus

$$\text{(2A)} \qquad F\ (\text{kidney}) = \frac{I\ (\text{kidney})}{\text{Area}\ (\text{Iliac})}$$

It remains then only to determine the I (kidney) or the total amount of indicator entering the kidneys in order to calculate F (kidney).

The method of determining I (kidney) is to allow the I (kidney) to be mixed with another known volume in the right side of the heart and to determine the resultant concentrations after dilution with that volume. The volume diluting the I (kidney) is the total return to the heart or the cardiac output.

Again, according to the basic theory

$$I\ (\text{kidney}) = F\ (\text{heart}) \times C \times t$$

or

$$\text{(3)} \qquad I\ (\text{kidney}) = F\ (\text{heart}) \times \text{Area (pulmonary artery)}$$

The pulmonary artery curve area can be experimentally directly determined. The $F_{(heart)}$ can be determined by introducing another known I into the heart and determining the area downstream in a peripheral artery. Thus

$$\text{(4)} \qquad F_{(heart)} = I_{(heart)} \div \text{Area}_{(peripheral\ artery)}$$

Knowing $I_{(heart)}$ and $\text{Area}_{(pulmonary\ artery)}$ we can calculate $I_{(kidney)}$ according to Equation (3).

Knowing $I_{(kidney)}$ and $\text{Area}_{(iliac)}$ (which is $\text{Area}_{(renal)}$) we can now calculate renal flow from Equation (2A).

In summary, we have determined the area of the time-concentration curve in the blood entering the kidneys from the iliac artery samples after injecting into the aorta above the kidneys; we have determined the total amount of indicator entering the kidneys by determining the area of the time-concentration curve produced when this indicator is mixed with the known total flow through the heart; we calculate the renal blood flow as the amount of indicator passing through the kidneys divided by the area of the time-concentration curve in blood entering the kidneys.

The validity depends on (1) representative sampling of iliac blood, (2) no recirculation of other indicator-containing blood during the determination of the pulmonary artery curve (coronary and brachiocephalic recirculation have been avoided by using injection into the descending aorta), and (3) a renal transit time sufficiently rapid to permit instantaneous injection of the indicator passing through the kidneys into the inferior vena cava.

Procedure

Comparison of renal blood flow determined by indicator dilution and clearance methods. Twelve experiments were performed in 11 mongrel dogs anesthetized with pentobarbital. Nylon catheters (O.D. 0.44 inch, I.D. 0.29 inch) were passed into the right atrium from the jugular vein. The thoracic aorta was catheterized retrogradely via the femoral artery. Initially the thoracic aortic catheter was fluoroscopically visualized by means of a wire within its lumen, but equally accurate placement could be made by determining from external measurements of the individual animal the necessary distance for insertion. The pulmonary artery was catheterized via the jugular vein with a National Institutes of Health No. 7 angiocardiographic catheter. Arterial curves were drawn through a polyethylene tube threaded into the iliac artery via the femoral artery. In 2 animals a catheter was placed in the right renal vein. In half of the animals a drip of 5 per cent mannitol or the administration of 15 to 30 c.c. per kilogram of warm 0.5 normal saline via a gastric tube was used to obtain adequate diuresis. Animals were sacrificed at the end of the procedure and the positions of the catheters were verified. The amount of indocyanine green indicator injected was calibrated by dilution volumetrically with 1 per cent human plasma in distilled water. Transmission was measured on a Beckman Model B Spectrophotometer at 800 mμ and compared with standard curves from weighed samples of indocyanine green. No allowance for impurities was made.[1,2] Calibration of the densitometer amplifier channels was made by the tripping technique of Emanuel and associates.[4] The range of sensitivities used on the arterial channel was 0.2 to 1.2 mg per liter per millimeter (as plasma). Sensitivities of 0.025 to 0.075 mg./L./mm. were

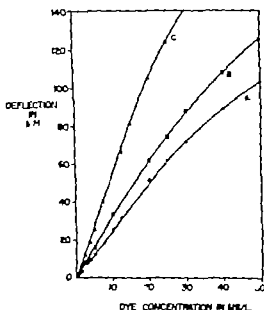


Fig. 1. Three calibration curves (A B C) in whole blood indicate the response of the arterial dyehead and densitometer unit to increasing concentration of indicator (indocyanine green). The variation in deflection for a given concentration is due to the deliberate use of different amplifiers for the output of the densitometer.

used on the pulmonary artery channels. In the latter range the trapping technique without crossover stopcocks (to allow for a maximum concentration of trapped dye) was valid only when blood levels at the initiation of the curve were low and stable. Base line blood levels of indocyanine were never above 3 mg. per liter and were only once noted above 2 mg. per liter. Peak height of the curve was never greater than 25 mg. per liter in arterial blood and exceeded 18 mg. per liter in only 2 animals. Peak heights of the pulmonary artery curve never exceeded 5 mg. per liter. Injectates were in the range of 0.025 to 0.1 mg. per kilogram. The linearity of the instrument used was tested in the proper range with whole blood. Three calibration curves of the response of the arterial densitometer unit to increasing concentrations of indocyanine green in whole blood are seen in Fig. 1. At three different amplifications linearity of response is shown below 20 mg. per liter with only a 2 to 3 per cent deviation

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from linearity at 25 mg. per liter. Above this point the deviation increases. The withdrawal sampling rate was 0.25 c.c. per second through catheters with volumes that varied from 0.5 to 1.1 c.c. In 2 animals para-amino hippuric acid (PAHA) was mixed with indocyanine green and after injection into the thoracic aorta curves were drawn from the pulmonary artery through cross-over stopcocks. In this manner blood was collected separately from the portion of the recirculation curve which represented renal blood flow. Alternatively, withdrawal curves from the pulmonary artery were discontinued during their exponential downslopes. Peak heights of PAHA concentration in the renal inflow blood were kept below 4 mg. per cent. PAHA was determined by standard technique except for the low concentrations given in Table III. Here dilution of the filtrate from the acid zinc sulfate protein precipitation was omitted in order to increase the sensitivity of the method.

In 1 animal from each of the above mentioned groups curves were drawn from the right renal vein after injection into the thoracic aorta.

Results

From the 12 experiments there were 40 pairs of valid measurements of renal blood

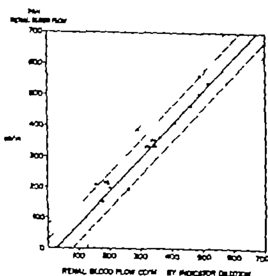


Fig. 2. The comparison of 40 pairs of determinations of renal blood flow yield the estimating equation Y = 28.4 + .9107X

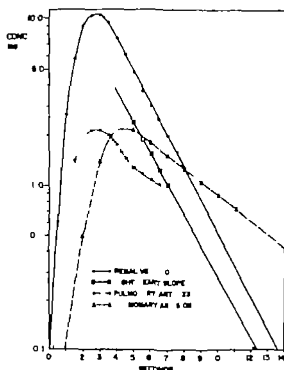


Fig. 3. Dog No. 16. Renal vein curve 5.08 was obtained after injection into the thoracic aorta and withdrawal from the renal vein. It is fortuitously similar to the right heart slope (see text). Pulmonary artery curves resulted from injection into the thoracic aorta and withdrawal from the pulmonary artery. A valid curve (*Pulmonary Art. 4.23*) has a slope slightly slower than renal vein or right heart slopes. Pulmonary artery curve 5.08 was recorded when renal blood flow had fallen relatively more than splanchnic flow.

flow which are listed in Table I. The estimating equation

$$X = 28.4 + .9197 Y$$

relating these values is shown in Fig. 2. The standard deviation is 36.2 c.c. per minute. The renal recirculation curves from a pulmonary artery withdrawal site in a given animal had relatively consistent slopes. Table II gives the average slopes of the total output curves determined in the usual manner and the renal pulmonary curves when two or more curves were derived from a single animal. No statistically significant differences separated the range of standard deviation of the pulmonary slopes from that of the total output slopes (Table II). Curves inscribed by injection of indicator into the right atrium and withdrawal from the pulmonary artery were slightly *faster than the renal recirculation curve* in the pulmonary artery. The renal vein slopes in 2 animals through a different withdrawal system were also slightly faster. The difference in slopes was not sufficient to indicate which, if either, was dominant, particularly in view of the different withdrawal systems. With the low flow to volume ratio used, no estimates of volume would be valid. Fig. 3 shows these various slopes—right heart, renal, true renal pulmonary, and a renal pulmonary (5.08) curve presumably distorted by splanchnic flow—from a single animal. Some original curves are seen in Fig. 4.

When PAHA was injected simultaneously with indocyanine, estimates of the expected pulmonary artery concentrations of PAHA were made from the ratios of the concentrations of the two indicators in the iliac curves and on the assumption that 88 per cent of the PAHA would be extracted from blood passing through the renal circulation. Expected and observed values of PAHA from areas of the recirculation curve beyond its exponential downslope presumably including indicator not of renal circulatory origin are also noted. Calculations in the latter case are based on iliac concentration ratios with no allowance for the extraction of PAHA. Table III shows the comparison



Fig. 4. Unplotted curves illustrate a better than average separation of renal and splanchnic flow (*Above*, curve withdrawn from pulmonary artery) and a typical iliac artery curve (*below*) after injection of indicator into the thoracic aorta.

Table I. Renal blood flow in milliliters per minute

Animal	*Indicator dilution*	*PAH clearance*	*Animal*	*Indicator dilution*	*PAH clearance*
3	364	364	13	237	208
	345	353		186	192
	338	353		202	197
				225	193
4	456	432			
	520	493	14	411	411
				463	464
8	348	337		391	429
	347	332		437	465
	324	332		451	483
9	320	332	17	614	506
				528	545
9A	194	215		490	563
	187	215		535	517
	265	215			
	196	208	18	156	208
				228	184
11	241	208		217	183
	177	145		261	191
				189	200
12	380	348		216	173
	280	312			
	292	391	19	492	504
	297	306		468	488

[illegible] d (9A) [illegible] d (9) [illegible]

of the predicted and observed levels In Dog No 16 it could be predicted from the distorted downslopes that the pulmonary artery curves 2 35 and 2 55 would contain PAHA of *nonrenal origin*

Discussion

Several sources of error exist with the method described There is no proof that the iliac artery time-concentration curve will yield the same area as would the time concentration curve entering the renal arteries after injection of dye into the thoracic aorta There is supporting evidence that mixing in the aorta is good[1,8] after a sudden injection against the stream and there is evidence that aortic flow is turbulent[8] One might suppose that renal arteries would sample more of the outer layer of aortic blood and that indicator might stream more in the center At any rate if the renal arteries received proportionately less indicator than the iliac arteries the renal blood flow would be underestimated by this method

If the curve obtained from the pulmonary artery after injection into the aorta contains dye from sources other than the kidney the renal blood flow will be over estimated

Comparison of a method which measures flow over a period of a fraction of a minute with a method (clearance) which measures flow over a period of many minutes will show considerable variability The single indicator method requires two injections which are not simultaneous Fluctuations in cardiac output and renal blood flow from minute to minute will be included in the comparison However on the whole if these fluctuations are random the average indicator renal blood flow approaches clearance values Random differences might be eliminated if comparison could be made with a method which measures renal blood flow over short periods of time On the assumption that both cardiac output and renal blood flow each vary as much as ± 10 per cent from minute to minute and on the assumption that both

the renal clearance and the indicator dilution technique may have over all errors of measurement of ± 5 per cent the correlation obtained between the methods is satisfactory

Difficulty in separating the renal curve from other splanchnic bed flows may occur if the renal circulation is reduced in excess of that to other areas The anesthesia (pentobarbital) may have reduced renal blood flow probably more than it reduced hepatic flow [7] Thus in the unanesthetized animal a clearer separation of renal and splanchnic curves may be possible Ideally one would like to find an indicator which could be identified as having passed through

Table II Variations in the slope of renal recirculation (pulmonary artery) curves and total output (peripheral) curves

Dog	*Renal recirculation curves (average slope)*	*Total output curves (average slope)*
3	340	471
4	357	416
8	241	335
9	412	491
11	561	463
12	423	293
13	372	242
14	381	333
17	477	253
18	284	432
19	329	252
	±0 014	±0 018*

*Standard dev [illegible]

Table III

Animal	*Time*	*Primary curve of renal recirculation*		*Principally extrarenal recirculation*	
		Calculated PAHA maximum with 88 per cent clearance (mg %)	*Observed PAHA plasma level (mg %)*	*Calculated PAHA maximum without clearance (mg %)*	*Observed PAHA plasma level (mg %)*
15	2 35	0 03	0 01		
	2 55	0 01	0 01		
				0 08	0 06
	3 13	0 01	0 01		
				0 11	0 11
	3 23	0 01	0 01		
				0 13	0 12
	4 12	0 01	0 02		
16	2 35	0 01	0 03		
	2 55	0 01	0 02		
				0 17	0 16
	3 45	0 04	0 03		
	4 23	0 03	0 01		

the kidney At the moment however separation of renal recirculation from that of other areas can be done only on a time configuration basis Tagging renal flow by PAHA removal is reassuring but unsatisfactory for quantitation We need to find some substance which is easily measurable in the pulmonary artery blood

Summary

A method is described for measuring renal blood flow using single injections of indicator into the right side of the heart and thoracic aorta with measurements of the time concentration curves which result in the terminal aorta and in the pulmonary artery

Determinations by the indicator method were compared in dogs with renal blood flow measured by the plasma clearance of para amino hippuric acid

The theoretical and practical technical aspects of the indicator-dilution method are presented and discussed

I wish to express my gratitude to Dr E V Newman Dr W W Lacy and Dr W Puckett for their suggestions and criticisms

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Case reports

Salmonella myocarditis

Report of a case with ventricular rupture

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The heart appears to withstand the blood-borne infection more effectively than do most other tissues of the body. Nonetheless, it may be injured by a wide variety of infectious agents, some of which have a greater virulence than others.[1] Among the infrequent invaders are members of the Salmonella family. For this reason it seemed appropriate to describe a case of acute myocarditis stemming from an overwhelming septic infection with *Salmonella choleraesuis*. Death resulted from rupture through an extensively inflamed area in the wall of the right ventricle, with bleeding into the pericardial sac and acute cardiac tamponade.

Case report

A 62-year-old Negro woman was admitted to the District of Columbia General Hospital complaining of loss of appetite and shortness of breath. During the preceding 3 weeks she had noted increased breathlessness and pain in the left anterior chest. She developed anorexia and frequent diarrheal stools 3 days before seeking medical attention. There were no other gastrointestinal complaints. There was no history of chills, fever, rash, cough, or pleurisy.

A diagnosis of hypertensive heart disease had been made in the past. For 2 years she had been continuously on digitalis and chlorothiazide therapy. One year before admission she was found to have fasting hyperglycemia and was placed on tolbutamide. One sister also had diabetes mellitus. The patient had been overweight for many years and chronically complained of pains in both knees. A complete hysterectomy because of uterine fibroids had been performed when she was 49 years old. The medical history was otherwise noncontributory.

Physical examination revealed a markedly obese woman who was sitting upright in bed in some respiratory distress.

The blood pressure was 150 mm. Hg systolic and 66 diastolic. The pulse was 110 per minute with occasional extrasystoles; the temperature was 101° F. (orally), and the respirations were 30.

There were coarse râles at the base of both lungs

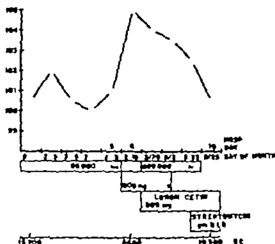


Fig. 1. Clinical course.

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Fig 2 The epicardium of the right ventricle is heavily infiltrated by an acute inflammatory process composed predominantly of small lymphocytes and macrophages (X66)

The left border of the heart extended to the anterior axillary line in the fifth intercostal space No murmurs were heard The liver was percussed 3 cm below the right costal margin There was a marked kyphoscoliosis of the thoracic spine Small freely movable lymph nodes were noted in the anterior cervical chain Findings in other parts of the examination were considered to be normal

An admission hematocrit was 37 per cent The white blood cell count was 15 700 with 79 neutrophils 19 lymphocytes and 2 monocytes Other laboratory tests including blood urea nitrogen fasting blood sugar bilirubin alkaline phosphatase and serum electrolytes were normal Febrile agglutinins drawn on the tenth hospital day revealed a Salmonella O titer of 1 40 A chest x-ray film confirmed the deformity of the thoracic spine and the enlarged heart An electrocardiogram demonstrated a sinus tachycardia ventricular extrasystoles and nonspecific flattening of the T waves

The patient's febrile course and mode of therapy is depicted in Fig 1 Cultures of three samples of blood obtained on the fifth hospital day contained gram negative rods identified as *Salmonella choleraesuis* Despite antibiotic therapy the patient deteriorated rapidly and died quietly on the tenth hospital day

Autopsy data The relevant autopsy findings were confined to the heart and reticuloendothelial system The pericardial sac contained 100 c c of blood and there were diffuse fibrinous deposits on the pericardial surfaces The heart was flabby slightly dilated and weighed 350 grams There was a rent through the thinned-out apex of the right ventricle A mural thrombus attached to the endocardium of the right ventricle had shed multiple emboli to both lungs



Fig 3 The myocardium of the right ventricle is involved by a mixed cellular reaction containing both inflammatory cells and large immature lymphocytes Vacuolization and disruption of muscle fibers are apparent



Fig. 4. The endocardium of the right ventricle is permeated by tumor cells intermingled with immature lymphocytes. (X94.)

Microscopically, there was an intense inflammatory reaction within the myocardium. In some areas the cellular response composed predominantly of small lymphocytes and macrophages involved the entire depth of ventricular muscle (Figs. 2-4). Some sections also contained large immature lymphocytes which presumably had migrated directly to the right ventricle from large mediastinal nodes (Figs. 3 and 4). A transmural fistula developed in such a thinned-out, heavily involved area of the right ventricle.

There was gross enlargement of the peripancreatic, mediastinal, and mesenteric lymph nodes. Histologically, the lymph nodes showed disruption and obliteration of normal architectural patterns by the rapid proliferation of large bizarre lymphocytes. The alterations in cell morphology and the invasive nature of the tumor were characteristic of a lymphocytic lymphosarcoma.

Discussion

The heart is infrequently involved during the course of clinically apparent Salmonella infections. Isolated reports have incriminated certain types of Salmonella as the cause of pericarditis,[2,3] valvular endocarditis,[1,3,4,6] infected mural thrombi,[7,8] mycotic aneurysms of the sinus of Valsalva,[1] and transient supraventricular arrhythmias.[9] Acute myocarditis as the dominant expression of the underlying infection is exceedingly rare.[10] However, a careful examination of autopsy material from case reports of Salmonella endocarditis reveal that the myocardium usually shares in the underlying inflammatory process.[1,3,4,6]

Saphra and Winter[5] evaluated the clinical manifestations in over 7,000 cases of Salmonella infections between 1940 and 1955 and found only 20 instances of bacterial endocarditis. No mention of myocarditis was made. Over half of those with focal cardiac lesions were due to the *Salmonella choleraesuis*. It has been recognized for many years that this is the most virulent member of the Salmonella family and notoriously predisposes to the formation of abscesses. The virulence of this organism is underscored by a 20 per cent mortality, which is far in excess of that due to other Salmonella types, and which has been imperceptibly altered by the advent of broad-spectrum antibiotics.[5] The presence of diabetes, sickle-cell disease, or, as in the case of our patient, an underlying malignancy enhances the appropriate setting for invasion by this organism.[11]

Myocardial rupture is an unusual feature of acute pyogenic myocarditis. Only a few examples could be culled from the literature.[1,12] The right ventricle, being a thin-walled chamber, is most susceptible to such a catastrophe. In our patient, death occurred from extravasation of blood through the fistula with acute cardiac tamponade.

Summary

Acute myocarditis is an unusual expression of Salmonella septicemia. *Salmonella cholerae-suis*, because of its inherent virulence, is most often incriminated as the cause of serious focal disease. A case of overwhelming invasion by this organism in a patient with underlying malignant disease is presented. The terminal event of cardiac rupture through an area of myocardium heavily infiltrated by tumor and inflammatory cells is of particular interest. The unusual aspects of this case are discussed briefly.

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Prolonged shock after myocardial infarction relieved by ACTH and cortisone

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Shock is a frequent complication of severe attacks of myocardial infarction and requires energetic therapeutic measures. Vasopressor drugs have been of great value, but treatment is still unsatisfactory. It has been demonstrated that a marked diminution in cardiac output accompanies shock associated with myocardial infarction, as in other types of shock,[1] but in cardiogenic shock this is believed to be due to a marked weakness in myocardial contraction. Usually, in cardiogenic shock there is an increase in peripheral resistance, but in certain cases this is normal or decreased, which suggests the probability that a peripheral vascular mechanism may also play a large role. The action of the adrenal corticoids in shock has not been convincing, although hydrocortisone is often used in an effort to potentiate the vasoconstrictor action of norepinephrine.

The case to be presented is of interest because of the long duration of shock—20 to 22 days—in a patient with myocardial infarction. (The term "shock" *is used in* the strictest sense, in that severe hypotension was associated with a cold, clammy skin, rapid thready pulse, and marked weakness.) Also, the electrocardiogram was not of the type usually associated with cardiogenic shock. Moreover, the dramatic response to ACTH and subsequently to prednisone suggests the possibility of temporary pituitary insufficiency and/or adrenocortical failure.

Case report

J. R., a 53-year-old white man, was in good health until 6 weeks prior to admission to the University Hospital on Sept. 1, 1961, when he suffered an attack of angina pectoris. On the morning of admission he developed severe crushing substernal pain which radiated to the left side of the back and left arm and required morphine for relief. This was accompanied by diaphoresis, faintness, and general weakness. The clinical impression was myocardial infarction. His past medical history was noncontributory.

On admission to the hospital he was in moderate distress. His blood pressure was 94/[illegible]0 mm. Hg and his pulse was 65 and regular. Examination otherwise was not remarkable. The heart was not enlarged; neither murmurs nor signs of congestive failure were present. He was treated with bed rest, Oxygenaire, anticoagulants, and Demerol for relief of pain. His hemoglobin was 15.1 Gm., white blood cells 14,300, of which 79 per cent were polymorphonuclears. Transaminase was 38 units. The patient vomited a few times during the first 24 hours. This stopped after he had received several oral doses (5 mg.) of prochlorperazine dimaleate (Compazine). The next morning, September 2, the blood pressure dropped to 72/60 mm. Hg, although his pulse remained slow and regular and he was free of pain. An intravenous infusion containing four ampules of Neo-Synephrine (40 mg.) in 500 c.c. of

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5 per cent glucose in water was started and his systolic pressure quickly rose to 120 mm. Hg. For the next 19 days intravenous infusions containing either the aforementioned drug or norepinephrine (four ampules (16 mg.) per 500 c.c. of 5 per cent glucose in water) were needed to maintain his systolic blood pressure above 100 mm. Hg. The electrocardiogram on admission (Fig. 1) showed changes that are usually associated with an ischemic pattern involving the anterior wall of the left ventricle rather than the extensive infarction that is usually associated with cardiogenic shock. Serial tracings were made but not until September 11 did the electrocardiogram show small Q waves in Leads V and V suggestive of an infarction involving the lateral wall of the left ventricle. Thereafter the tracings remained essentially unchanged and were similar to that seen in Fig. 2 which was made before his discharge on Oct. 21, 1961.

The blood pressure dropped precipitously and on several occasions was unobtainable when the infusion of Neo-Synephrine or norepinephrine was stopped either to test the necessity for the vasopressor drugs or because of technical difficulties. The drop in blood pressure was associated with cold clammy skin, rapid pulse, and dyspnea. While on pressor drugs the patient was free of pain, was not dyspneic, and was very comfortable.

On the twentieth day, September 20, because it was thought that perhaps adrenal insufficiency accounted for the hypotension and other signs of shock, the patient was started on 20 units of ACTH intramuscularly every 8 hours. He responded to this, and within 24 hours his blood pressure was maintained at 110/70 mm. Hg with two drops per minute of a solution containing one ampule (4 mg.) of Levophed in 500 c.c. of 5 per cent glucose in water, a very marked decrease compared to that required before ACTH. On September 22 the pressor drugs were discontinued. On September 23 the ACTH was stopped and he was started on 10 mg. of prednisone every 8 hours and 0.1 mg. of 9 alpha fluorohydrocortisone (Florinef) daily. The prednisone was tapered so that on September 25 his total dosage was 25 mg.; it was 20 mg. on September 26, 15 on September 29, 10 on October 1, and 5 on the morning of October 3, so that adrenal function studies could be made. Because of the stormy course in the hospital it was thought advisable to continue him on small doses of Florinef—0.1 mg. daily.

Twenty-four hour collections of urine were obtained for estimation of 17-hydroxycorticosteroids, 17-ketosteroids, and gonadotropins. ACTH stimulation tests were also done. The results of these tests are shown in Table I.

Other laboratory studies showed that his protein-bound iodine was 3.8 mcg. per 100 ml., serum sodium was 133, potassium 4.5, chlorides 101, and carbon dioxide 28.6 mEq. on September 22. His blood sugar and urea nitrogen were normal. X-ray examination of the skull demonstrated no significant abnormalities. The pineal was calcified, not displaced, and the pituitary fossa was normal, and no other abnormalities of bone or soft tissue were noted.

The patient was discharged on Oct. 21, 1961, in good condition. He was continued on anticoagulants and on prednisone, 5 mg. three times daily, and Florinef, 0.1 mg. daily. These drugs were continued as a precautionary measure. Thereafter prednisone was gradually reduced. He had no difficulty maintaining his blood pressure on 5 mg. of prednisone and 0.1 mg. of Florinef daily, but he found it difficult to continue his work as a salesman when these drugs were discontinued even for a few days. It was necessary to wait until Feb. 4, 1963—during a slack period in his business—before adrenal function studies could be repeated after 10 days without drugs. For several weeks after these drugs were stopped he experienced marked weakness; this gradually disappeared. Fig. 3 is the electrocardiogram made May 23, 1963.

Table I. Laboratory findings

Day	Volume (ml.)	Specific gravity	Creatinine	17–KS (mg./24 hr.)	17–OHCS (mg./24 hr.)	Gonadotropins (mouse units)
Control (Oct. 10-11, 1962)	3,500	1.009	1.7	12.9	Not detectable	>48<96
Control (Oct. 11-12)	2,800	1.008	1.8	12.6	Not detectable	
Day 1–ACTH stimulation (Oct. 16-17)	4,000	1.010	1.8	24.0	4.0	
Day 2–ACTH stimulation (Oct. 17-18)	4,100	1.011	1.1	38.6	4.3	
Day 3–ACTH stimulation (Oct. 18–19)	3,900	1.012	1.7	54.6	8.9	
Day after stimulation (Oct. 19–20)	4,070	1.011	1.3	16.4	Not detectable	
Feb. 14-15, 1963	2,700	1.016	1.5	5.7	6.2	>192

*Questionable accuracy because [illegible] the urine.

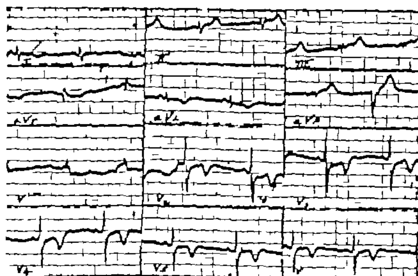


Fig. 1. ECG recorded on day of admission, Sept. 1, 1961.

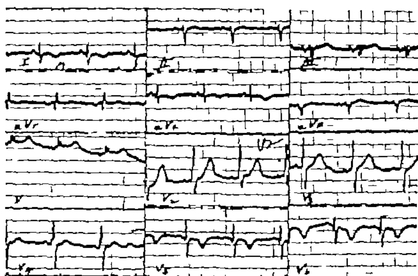


Fig. ECG recorded on Oct. 21, 1961, at discharge.

Discussion

Shock in myocardial infarction has been reported in approximately 10 to 20 per cent of the cases, with a mortality of 14 to 100 per cent. Obviously, the marked difference in mortality is probably due to the lack of uniformity in criteria in various reports and this would also explain the variable incidence of shock mentioned in these reports. To include patients who merely have hypotension without other evidences of shock, or cases of so-called impending shock, will increase the incidence and decrease the mortality. It has been our experience that in patients with myocardial infarction, shock may occur initially either in a marked or mild form; many of these patients recover rapidly, although in many others recovery from the initial shock does not take place. Shock may also occur during an arrhythmia with rapid ventricular rate, and here again control of the arrhythmia may often result in recovery.

However, the shock which occurs one or more days after the infarction may be

severe and persistent with a progressive drop in blood pressure and if not treated promptly may result in irreversible shock. It has been stated that shock of cardiogenic origin which lasts more than 4 hours is frequently irreversible and it is believed that in those cases which occur one or more days after the onset of myocardial infarction the shock is more frequently due to myocardial failure than to peripheral vascular collapse. Shock usually occurs in patients with extensive infarctions. In dogs Selzer and Taylor[3] could produce shock only by ligating the major branches of the left coronary artery which produced a massive infarct.

Our case is unusual in that signs of an extensive infarction were not present in the electrocardiogram although the ECG may not at times show the true extent of an infarction. However other indications of a massive infarction such as high fever, high leukocyte count, high transaminase or signs of congestive heart failure were not present. The long duration of shock in our case—20 to 22 days—is also very unusual. Except for the case reported by Backer, Dean and Iacello[4] that lasted 55 days in a 61 year old man with myocardial infarction, our case is in so far as we can determine the longest on record after coronary occlusion. These same authors report a case that lasted 22 days after operation and Townley and Brockley[5] reported a case of myocardial infarction with shock that lasted 19 days with eventual recovery, but in these cases after myocardial infarction the electrocardiograms showed evidence of extensive infarctions. We have observed 2 other cases, one in a 45 year old man and another in a 62 year old woman who developed hypotension and signs of shock for 11 and 8 days respectively, but who did not show evidence of extensive infarctions in the electrocardiograms. These patients improved on vasopressor drugs without ACTH and or cortisone and it is worthy of note that as in the case reported the prolonged use of relatively moderate doses of pressor drugs was required to stabilize the blood pressure.

It has been suggested that shock of cardiac origin may be related to inadequate adrenal cortical reserve and conversely adrenal cortical hypertrophy is said to be present in myocardial infarction without shock. Klein and Palmer[6] however found the level of plasma 17 hydroxycorticosteroids to be normal or elevated in patients with myocardial infarctions with or without shock and therefore there is no theoretical advantage to the administration of exogenous cortisone. We have used cortisone preparations (and also ACTH) intramuscularly and intravenously combined with norepinephrine in patients suffering from cardiogenic shock but with questionable results.

In this case the marked improvement

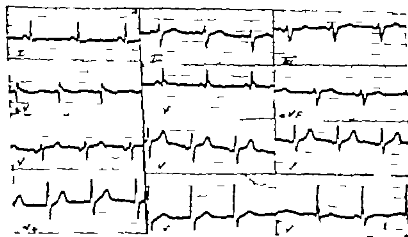


Fig. 3. ECG recorded on May 23, 1963.

followed almost immediately upon treatment with ACTH and then prednisone and Florinef. Eight days after a normal blood pressure had been achieved by means of the therapy outlined above, hormone studies were made (Table I). We did not consider it advisable in view of the patient's condition to stop all corticoids lest he go into shock again with possible disastrous results, and he was continued on 0.1 mg. of Florinef daily; we did not believe that such small doses of Florinef would materially influence the laboratory results. The excretion of gonadotropins in the urine was consistent with the patient's age. The 17-ketosteroids were well within the normal limits and responded to the administration of adrenocortotropin over the 3-day period. Urinary 17-hydroxycorticosteroids were reported to be "nondetectable" in the control urines before ACTH stimulation and the day after stimulation, but unfortunately the report of "nondetectable" urinary 17-hydroxycorticosteroids by the Peterson modification of the Silber-Porter technique was questionable inasmuch as a considerable amount of color-producing substance was present in the urine. Nevertheless, the evidence presented in the table indicates an increased excretion of phenylhydrazine-reacting substances, presumably cortisol metabolites, after the administration of adrenocorticotropin, suggesting two possibilities, both of which are speculative: (1) For unknown reasons there was a temporary pituitary insufficiency which produced secondary adrenal insufficiency during shock. (2) The striking improvement after large doses of ACTH and prednisone strongly suggests that they had produced some change in the responsiveness of the arterioles to norepinephrine, although there was no unequivocal evidence of adrenal cortical failure by hormone assay 20 days after the marked therapeutic response to these drugs.

The dramatic stabilization of the blood pressure after therapy with ACTH and subsequently cortisone leaves little doubt that these agents were in some manner responsible for the restoration of the stable blood pressure. The occurrence of shock in a patient whose attack was apparently mild, according to the electrocardiogram, the leukocyte count, transaminase, and the lack of high fever, suggests the probability that it may have been due to a cause different from that seen in the average patient with severe infarction. We have not observed such dramatic stabilization of blood pressure by ACTH and/or cortisone in many other cases of myocardial infarction associated with prolonged shock. In those patients in whom the blood pressure was finally stabilized, the effect of these drugs was questionable.

Summary and conclusions

1. The pertinent data of a patient with shock of at least 20 and probably 22 days' duration after myocardial infarction is presented.

2. There was a dramatic stabilization of the blood pressure after treatment with ACTH and subsequently prednisone and Florinef.

3. The electrocardiogram, temperature, leukocyte count, and SGOT were not those usually observed in cases of extensive myocardial infarctions in which shock is a frequent complication.

4. The occurrence of shock in patients without evidence of an extensive infarction is very uncommon and suggests that in such a circumstance shock may not be due to the same factors responsible for its development in patients with extensive myocardial infarction.

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Review

Coronary vasodilator therapy for angina pectoris

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The classic descriptions of angina pectoris established a clinical entity which is now well known to all physicians and to most laymen. Although the pathologic physiology of this defect has been elucidated more slowly, it now rests on firm theoretical grounds with general acceptance of the analogy of anginal pain to the pain in an extremity in which the arterial blood supply is compromised. Indeed, few would seriously question that the malady results from a discrepancy between the amount of attainable blood flow in a region of the myocardium and the amount required to sustain a given degree of activity, i.e., the familiar economic problem of supply and demand. Data have continued to accumulate, however, which support this pathophysiologic concept and which may be considered as a guide to the therapy of angina pectoris consequent to coronary atherosclerosis.

Study of subjects with angina pectoris by the nitrous-oxide method has demonstrated that resting coronary blood flow per unit of weight of myocardium is normal.[1-3] Although this finding has been disturbing to both clinician and investigator since no other satisfactory method is now available for the study of coronary blood flow in man, some effort should be made to reconcile this data with our primary hypothesis of reduced flow. It is possible that the area of muscle in which ischemic pain arises is small in relation to the general myocardial mass and that its reduced flow is lost in the error of the nitrous-oxide method. Furthermore, it is probable that reduction of coronary blood flow below the basal resting level for a significant period does not permit survival of the myocardium and that severely ischemic areas are replaced by scar tissue. The nitrous-oxide method is assumed to measure flow per unit weight of perfused surviving myocardium; therefore, the scarred areas might not be fairly represented in the over-all result. As a result of experiments in which nitroglycerin failed to produce an increase in coronary blood flow of subjects with angina pectoris,[2] it was considered that although normal at rest their coronary flow could not increase to meet increased metabolic demands,[4] but more recent studies have shown that during exercise coronary blood flow of patients with angina increases as much[1] as or even more[5] than it does in the normal person. However, the coronary sinus oxygen content of subjects with angina does not increase with exercise as it does in normal subjects.[4,5] It may be postulated, therefore, that whereas coronary flow increases in certain areas of the atherosclerotic heart during exercise, in other areas in which the coronary vessels are diseased flow does not increase as much as required to meet the metabolic de-

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mands. Probably the oxygen content of the coronary venous blood draining from underperfused segments is significantly lowered and anaerobic metabolism occurs. If this is the case, the specimen of mixed cardiac venous blood should reveal the composite of blood from those areas in which venous oxygen content is increased and those in which it is decreased, and the oxygen content of the mixed specimen might well remain the same or fall slightly. These considerations appear then to remove or reduce what appears at first to be a discrepancy between theoretical considerations and reported observations.

Hemodynamic studies made after the administration of agents used therapeutically for angina pectoris have also led to several disturbing and rather discordant observations. Thus, whereas it has been reported that the administration of nitroglycerin to subjects without coronary artery disease or increased left ventricular work augmented the coronary blood flow, the coronary sinus blood oxygen content did not rise and myocardial oxygen consumption increased.[11] This latter observation is somewhat disturbing in view of the fact that cardiac oxygen utilization did not increase during the administration of nitroglycerin to experimental animals[12] or to subjects with angina pectoris and or increased left ventricular work.[7] Furthermore, nitroglycerin did not increase the coronary blood flow in subjects with angina pectoris or with increased left ventricular work.[7] Erythrol tetranitrate did not increase coronary blood flow either in normal subjects or in subjects with angina pectoris.[8] There seems to be no reasonable doubt that nitrites produce dilatation of the coronary arteries as revealed by angiographic studies in experimental animals[13] and in man (Sones). Data using objective methods in the dog have frequently indicated increased coronary flow with nitroglycerin; however, all experiments in which the agent is introduced into the coronary vessels in a concentration higher than that present in peripheral vessels must not be considered to be representative of clinical administration. Similarly, all studies in which arterial perfusion pressure is maintained constant during the action of the drug represent artificial conditions in that they do not reproduce the effects of clinical administration. Abstract contemplation of the problem would indicate that any vasodilator should increase flow if pressure is sustained unchanged; unfortunately, this is not the case with the clinical administration of nitrites, and the demonstration of vasodilatation during the hypotensive phase of drug action must not be equated with increased blood flow. Furthermore, the marked physiologic effects of contrast substance administered both systemically[14] and into the coronary arteries[15] cannot be ignored, and make it even more difficult to interpret angiographic studies.

Some hypotensive agents reduce the frequency of attacks of angina pectoris in subjects with arterial hypertension, provided that the fall in blood pressure is not excessive. This is reported for the ganglion blocking drugs[16] in spite of the fact that they usually reduce coronary blood flow.[17,18] In doses which do not cause excessive hypotension, hydralazine increases coronary blood flow and the coronary sinus blood oxygen content.[19] However, its administration to subjects with angina pectoris is reported on occasion to precipitate attacks of anginal pain.[1] Intravenous administration of adenosine triphosphate (ATP) and other adenine nucleotides to intact animals produces a remarkable increase in coronary blood flow with a marked increase in the coronary sinus oxygen content.[20] Although there are reports of successful trials of ATP in the therapy of angina pectoris, the doses used were so small that it is doubtful whether they were active.[2,4] Furthermore, the administration of ATP has produced a sensation of constriction in the chest and considerable discomfort deep in the chest.[3,4] ATP has not been regarded as being useful in the therapy of heart disease—indeed perhaps harmful.[7] Dipyridamole (Persantin) has been shown to produce coronary vasodilatation with increased coronary blood flow.[21,6] There is strong suggestive evidence that its effect may be mediated through inhibition of the activity of adenosine deaminase, thereby effecting longer activity of normally released adenosine.[22] Yet clinical use of this agent has been disappointing in the therapy

of angina pectoris.[14, 16] There appears then to be no predictable relationship between the effect of a drug on over-all coronary blood flow and its effect on angina pectoris.

Pathologic studies have shown that, statistically speaking, a subject with angina pectoris has suffered occlusion of at least one coronary artery,[38] and frequently has a patchy distribution of normal and narrowed sclerotic or occluded coronary arteries. If this atherosclerotic narrowing becomes a major factor in determining myocardial blood flow, and it seems reasonable that it does, it is difficult to conceive of any agent which could produce dilatation of the rigid or occluded areas in the tubes which presumably supply blood to the pain-producing areas in the heart. Therefore, it seems doubtful that effective agents relieve anginal pain by coronary vasodilatation that produces increased coronary blood flow, and some other mechanism should be considered.

It was postulated by Brunton[41] when he introduced amyl nitrite into the therapy of angina pectoris that the agent was effective because it lowered blood pressure and hence decreased cardiac work. Cardiac output falls subsequent to the administration of erythrol tetranitrate accompanied by decreased systemic arterial pressure and reduced left ventricular work.[4] Similar results were described in the subjects who received nitroglycerin.[7] When chlorothiazide lowers the blood pressure of hypertensive subjects with angina, their pain is frequently reduced,[17] even though it has been demonstrated in man that the drug does not increase coronary blood flow.[1] Chlorothiazide acts acutely to reduce cardiac output[44] and chronically to reduce peripheral vascular resistance,[46] hence decreasing cardiac work. Similarly, the ganglion-blocking drugs decrease or do not change coronary blood flow, whereas cardiac work is significantly reduced.[7, 18] The induction of hypothyroidism has been reported to be successful at times in reducing the severity of anginal pain, even though a decrease in thyroid activity, such as that produced during therapy of thyrotoxicosis, is known to be associated with a decrease in coronary blood flow.[49] In 3 subjects who were relieved of angina pectoris by an amine oxidase inhibitor, neither cardiac rate, blood pressure, nor cardiac output increased normally in response to exercise.[41] All of these observations fit with the concept that relief of angina pectoris is obtained not by increased coronary blood flow, but by the reduction of left ventricular work into a range which can be supported by attainable myocardial circulation.[6, 7]

How does such a concept influence our general philosophy concerning coronary vasodilators in subjects with angina pectoris? First, therapy of the acute attack of angina pectoris should be directed at reducing cardiac work. Most subjects discover very quickly that relief from anginal attacks can be obtained by cessation of exertion with motionless standing. Thus blood is pooled in the dependent portion of the body, cardiac output is reduced, and cardiac work is brought into the range of myocardial blood supply. The same result may be obtained pharmacologically by the administration of the short-acting vasodilator nitroglycerin. Second, biologically available coronary vasodilators (adenine nucleotides,[3] dopamine,[4] catecholamines, etc.) increase coronary blood flow considerably more than do any of the agents which have been available clinically. Although it has not been established that the adenine nucleotides are available to act as coronary vasodilators, it seems very probable that when the cell is compromised by ischemia, accumulation of lactic acid and carbon dioxide, these compounds may diffuse into vessels of the injured area. Furthermore, if these compounds are released, they enter not into the general circulation, where their activity is dissipated uselessly on vessels which do not require dilatation, but where ischemia is most intense and therefore where a coronary vasodilator would do the most good. Third, subsequent to occlusion of a coronary artery, collateral channels grow into the area which has been rendered ischemic. The most potent stimulus to the development of collateral circulation is probably graded ischemia and therefore carefully controlled exercise. The data which relate the incidence and severity of coronary artery disease to physical activity show that the heavier the work a subject does, the less extensive

is atherosclerotic heart disease and the smaller and less frequent are scars in the myocardium.[43] It would be foolhardy to argue that collateral vessels are not capable of dilatation and constriction for indeed their dilatation has been clearly demonstrated by Sones and Shirey but it may be questioned whether under the impelling stimulus of the ischemia which promotes their growth they would respond to extraneous pharmacologic agents with significant further dilatation or increased flow. Fourth since the vascular bed is a series of parallel circuits during vasodilatation the aortic head of blood pressure is dissipated into the most readily distensible vessels. Furthermore rigid vessels are dependent for perfusion solely upon the pressure to which they are exposed and during hypotension will almost inevitably receive reduced flow. This may well explain the occasional paradoxical effect of nitroglycerin[44] and the occurrence of infarction during excessive or prolonged hypotension in subjects with angina.

It is suggested that those who seek therapeutic agents for angina pectoris might try drugs which temporarily reduce cardiac work. It could be enlightening to consider whether these agents should or should not be vasodilators since it does not seem reasonable that any systemically administered agent would single out a localized area of badly diseased vessels and produce a specific dilatation of these sclerotic even bony tubes in preference to soft pliable vessels readily capable of vasomotion. Furthermore it would seem unreasonable to use long acting agents which are potentially detrimental through dilatation of normal vessels for prolonged periods of time thereby reducing the pressure head available to diseased vessels or through reduction of cardiac work over an extended period thereby reducing the normal *stimulus to the growth* of new vessels. It is conceded that *immediately* after myocardial infarction long acting nitrites may increase the length of survival of experimental animals.[45] It is not known how this is accomplished although it may well be through prolonged reduction of cardiac work since the degree of physical activity may be difficult to control. Such data do not necessarily indicate that similar treatment would be beneficial in the case of chronic coronary artery disease in man and must be gathered from man himself before they can be properly interpreted.

In general it is accepted that although the lesions are irregularly distributed coronary artery disease is progressive—indeed almost inexorable in some subjects. It is agreed that the goal of therapy for this process should be the re establishment of a normal lumen in the diseased vessels. Unfortunately this ideal does not seem to be attainable at present. In the meantime it would seem to me that the role of the physician in the vasodilator therapy of angina pectoris consequent to coronary artery disease is not that of a prime actor but rather of a supporter who intervenes only when forced to do so and then only for as short a time as possible in order to relieve pain through temporary alteration of the discrepancy between demand and supply in the heart. When he does intervene the physician might consider vasodilator therapy as supplying symptomatic relief which does not alter the course of the disease but which permits his patient to proceed slowly and laboriously with these temporary interruptions toward development of collaterals as the best current solution of his localized vascular problem.

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Electrocardiographic alterations associated with electrically "silent" areas of myocardium

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Death of electrically active ventricular myocardium results in a loss of cardiac electromotive force (emf) which in turn results in disturbances in the time course of ventricular depolarization. The loss of electromotive force may be manifested in the electrocardiogram by (1) development of abnormal Q or QS waves, (2) changes in the amplitude of R and S waves, and (3) development of abnormal notching or slurring of any or all components of the QRS complex. The electrocardiographic alterations in any one lead depend upon the position of the lead electrode(s) relative to the spatial orientation of the area of infarction. Great emphasis has been placed on the clinical and experimental study of electrocardiographic manifestations associated with death of myocardial tissue. On the other hand, relatively little attention has been directed to the study of the electrocardiographic alterations which occur when a portion of the myocardium which is still viable fails to undergo electrical activity. Nevertheless, it was demonstrated many years ago that cardiac action potentials could be increased or decreased by altering the electrolyte content of the fluid bathing the heart.[1] The fact that under the proper experimental conditions action potentials from cardiac muscle can be eliminated and then restored (2) is clear evidence that loss of electromotive force is not synonymous with tissue death. Nevertheless, there is a general tendency to equate loss of electrical activity as manifested in the electrocardiogram with nonviability or death of myocardial cells.

The term "electrically silent" has been used in the past to describe dead electrically inactive myocardial tissue[3] as well as to describe areas of the myocardium which, when infarcted, fail to produce electrocardiographic evidence of infarction.[4] However, in the anatomic sense, dead myocardial tissue may be present for only a short time before it is replaced by electrically inactive but not dead fibrous tissue. Thus the term "electrically silent," when used to described loss of myocardial tissue in an area of infarction, actually refers to replacement of myocardial tissue with electrically inactive fibrous tissue and does not describe a physiologic state of the myocardium. In the case of myocardial tissue which fails to produce electrocardiographic changes when infarcted, such tissue is almost certainly not electrically silent. The lack of electrocardio

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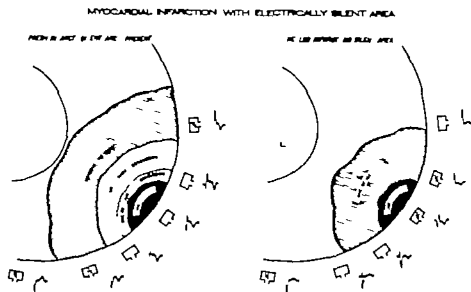


Fig 1 Schematic representation of the influence of a theoretical zone of "concussion" on the configuration of the precordial electrocardiogram Consult text

graphic manifestations of infarction in such instances is due to inadequate sensitivity of the recording system rather than to electrical silence For example there is no reason to doubt that the usual electrophysiologic alterations associated with infarction occur in an intramural infarction However the abnormal electrical forces do not necessarily produce recognizable changes in the electrocardiogram Such an area is electrically hidden (using conventional electrocardiographic methods of recording) but is by no means electrically silent Obviously an electrically silent area may also be electrically hidden

We have arbitrarily defined in this presentation an electrically silent area of myocardium to be an area of myocardium which does not undergo depolarization and repolarization but which is not dead and which under the proper circumstances may recover and again become electrically active It is also evident that an area of myocardium which is electrically silent is also mechanically silent and fails to contract during the cardiac cycle

The purpose of this paper is to describe various electrocardiographic alterations which occur as a result of the presence of electrically silent areas within the myocardium These discussions are based largely upon impressions gained from correlation of the electrocardiogram with the autopsy findings in more than 5 000 patients As these discussions will indicate very few experimental studies on electrically silent areas have been performed

Myocardial concussion The electrocardiographic patterns associated with acute myocardial infarction are well known However for purposes of orientation the mechanisms responsible for these changes in a unipolar precordial electrode placed directly over an area of infarction are described briefly below Of course these considerations with the proper modifications pertain to all leads whether unipolar or bipolar

After sudden coronary artery occlusion and in the absence of an adequate collateral circulation the portion of the myocardium supplied by the occluded coronary artery becomes infarcted The infarcted area consists of several physiologic zones viz a zone of tissue death a zone of tissue injury and a zone of tissue ischemia[1] Obviously within the zone of tissue death all electrical activity ceases so that the net electrical potential recorded by an exploring electrode over the infarcted area is usually diminished when compared to the potential before infarction Thus after infarction the R wave registered by a precordial electrode placed over an area of infarction will be of smaller amplitude than that registered before the infarction

had occurred Depolarization continues to occur in the zone of injury and may even be accelerated but there is a decrease in the magnitude of the resting membrane potential The difference in potential between normal and injured cells results in a flow of current from the injured cells into the normal cells This current is known as the current of injury and is characteristically manifest in the electrocardiogram as an elevation in the S T segment Repolarization within the zone of ischemia is delayed and is initiated in the area of least ischemia which is usually near the endocardium rather than the epicardium so that the T wave recorded by a precordial lead over the infarcted area is inverted Thus the classic electrocardiographic manifestations of acute myocardial infarction involve the QRS complex the S T segment and the T wave[4]

The physiologic basis for the electrocardiographic changes which occur as a result of myocardial infarction are not yet completely understood despite many experimental studies with electrodes inserted directly into the myocardium or into single myocardial fibers However a large amount of electrophysiologic data indicates that the concept that an area of myocardial infarction may be divided into three physiologic zones is reasonably accurate Although experimental proof is lacking clinical observations suggest that besides the three classic zones there may be still another physiologic zone surrounding an area of infarction which we have termed the zone of myocardial concussion Within the zone of concussion the myocardial cells are so compromised that they do not undergo electrical activity but nevertheless are not dead Such cells are electrically but not biologically dead and possess the capability of recovering (Fig 1) With improvement in the coronary circulation and physiochemical repair the myocardial cells within the zone of concussion recover and electrical activity returns The time required for electrophysiologic recovery is variable

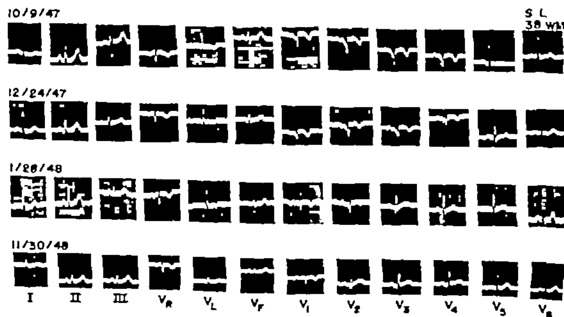


Fig Serial electrocardiograms showing recovery of the R waves in Lead V V and V after an acute myocardial infarction QS waves present in Leads V V and V on 1 /24/47 are no longer present on 1/28/48 Note particularly that between 1/28/48 and 11/30/48 a significant decrease in magnitude of the Q wave in Leads V V and V occurred The unipolar limb leads indicate that there was no change in cardiac electrical position during the recording of the electrocardiograms

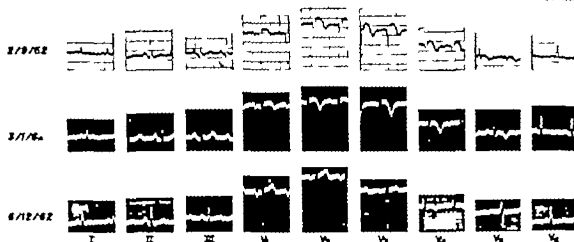


Fig. 3. The electrocardiograms recorded on 2/9/62 and 3/1/62 show loss of the R wave in Leads V[illegible], V[illegible], V[illegible], and V[illegible] as a result of an acute anteroseptal myocardial infarct. The electrocardiogram recorded on 6/12/62 shows regeneration of the R wave in Leads V[illegible], V[illegible], and V[illegible]. The return of the R wave is thought to be due to recovery of the zone of concussion. Recovery of the R wave in Lead V4 was already apparent in the electrocardiogram recorded on 3/1/62.

The electrocardiogram during the acute phase of infarction reflects loss of electrical potential from both the zone of myocardial death and from the zone of myocardial concussion. However, when the zone of concussion regains electrical activity, the electrocardiogram reflects both the electrical activity regained from the zone of previous concussion and the loss of potential from the zone of myocardial death (Fig. 1). Figs. 2, 3, and 4 are serial electrocardiograms from 3 patients with acute anteroseptal myocardial infarction. In each patient QS waves developed in several precordial leads. However, with time a gradual regeneration of R waves occurred in the precordial electrocardiogram. The recovery of electromotive force is considered to coincide with recovery of the electrical activity in the zone of myocardial concussion. Such recovery may occur within a few days or months after infarction. Although there is no direct experimental proof of the existence of a zone of myocardial concussion, studies by Rakita[6] and Conrad and associates[7] have shown that activation of myocardial cells rendered ischemic by coronary artery ligation may be delayed. It is not inconceivable that the delay in depolarization of ischemic cells is widely variable, with a brief delay in some cells, a longer delay in others, and complete absence of activation or depolarization in others.

On the basis of these considerations it is evident that judgment concerning the extent of a myocardial infarction on the basis of the electrocardiogram should be withheld until enough time has elapsed for recovery of the zone of myocardial concussion.

Development of pathologic Q waves during episodes of angina pectoris. Electrocardiographic patterns of infarction, particularly pathologic Q waves, may develop during episodes of otherwise typical angina pectoris.[8] The pathologic Q waves disappear after angina pectoris subsides. The physiologic basis for the appearance of pathologic Q waves during episodes of angina pectoris is unknown but is probably related to the development of electrically silent areas of myocardium due to the failure of ischemic cells to depolarize. The mechanism whereby ischemia electrically stabilizes the myocardial cell membrane is unknown. Such electrically silent areas

are also mechanically silent. The association of mechanical and electrical inactivity is well illustrated during episodes of myocardial insufficiency involving the anterolateral papillary muscle. Mechanical inactivity of the papillary muscle results in the development of a characteristic murmur which disappears after the episode of angina pectoris subsides,[9] thus providing a rare opportunity of correlating in intact man electrical and mechanical events by relatively simple means, i.e., an electrocardiograph and a stethoscope.

Reversible electrocardiographic patterns of infarction may also develop during cardiovascular shock or spasm of a coronary artery. Wilson and associates[19] cited the case of a patient in whom characteristic QRS changes of myocardial infarction had completely disappeared 1 month after they developed. Those authors postulated that the ischemic cardiac muscle was for a time incapable of responding to the excitatory process but it was not dead and subsequently recovered to excitability. That acute ischemia can produce electrical silence in the absence of morphologic changes (myocardial death) is indicated by the fact that pathologic Q waves have been observed to develop in the electrocardiograms of patients in whom detailed microscopic studies have failed to demonstrate any evidence of infarction (Fig. 5). Presumably in some instances the patient died before anatomic changes could develop.[1] Nevertheless, a portion of ap

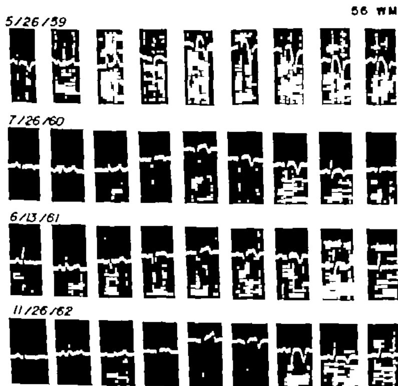


Fig. 4. Serial electrocardiograms of a patient with an extensive anteroseptal and lateral myocardial infarct. The electrocardiogram recorded on 5/26/59 shows almost complete loss of R waves in all precordial leads. However, well developed R waves are displayed in the electrocardiogram recorded 14 months later on 7/26/60. These tracings show that in so far as the electrocardiogram is concerned, judgment in regard to the extent of a myocardial infarct should not be made on tracings recorded during the acute phase of the infarct.

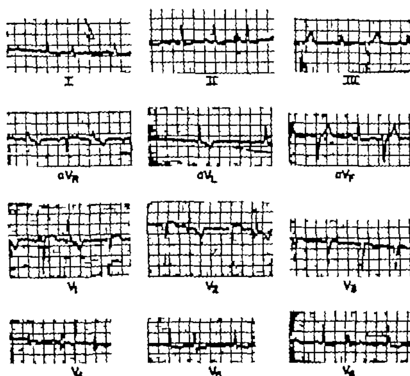


Fig. [illegible]. Electrocardiogram from a patient with ischemic heart disease and angina pectoris. The ventricular premature complexes in Leads V[illegible] and V[illegible] display pathologic Q waves. The patient died suddenly 2 days after the electrocardiogram was recorded. Postmortem examination demonstrated a fresh anteroseptal myocardial infarct.

Na^+ than to K^+ ions. The fully activated membrane would be permanently depolarized if P_{Na} remained greater than P_K. However, very soon after the peak of the action potential is reached, there is a progressive decrease in P_{Na} followed by an increase in P_K. The permeability of the membrane for sodium continues to decrease until it reaches the resting value. Coincident with the decrease in P_{Na}, there is a decrease in the contribution of E_{Na} and an increase in the contribution of E_K to the transmembrane potential, so that by the time the resting state is reached, E_K again dominates the transmembrane potential.

Applying the Hodgkin theory to the problem of electrical silence, one may reasonably assume that an electrically silent area can exist if (1) the membrane fails to undergo depolarization so that no action potential develops, (2) the membrane is depolarized but the resulting action potential is too weak to activate the neighboring membranes, i.e., the depolarizing impulse is not propagated, and (3) the membrane is depolarized and is propagated but the net emf is too small to be recorded by a surface electrode. There is some experimental evidence for at least some of these assumptions. For example, Hoffman and Suckling[9] obtained records of action potentials from single fibers immersed in Tyrode solution before and after the addition of KCl to the solution. They found that the amplitude of the action potential was dependent upon the magnitude of the resting potential. Increasing the concentration of KCl in the fluid bathing the cell caused an abrupt decrease in the resting potential and in turn a further decrease in the amplitude of the resting potential until there was a

complete loss of excitability. Washing the KCl away resulted in restoration of the resting potential and in turn of the action potential. When the resting membrane is depolarized by the addition of KCl to the extracellular fluid, the membrane is inactivated, an event which may occur in anoxia. Thus K^+ influences the action potential through its effect on the resting potential.

On the other hand, the concentration of extracellular sodium appears to effect the action potential more than it does the resting potential.[1,2] Lowering the concentration of extracellular sodium results in a decrease in the magnitude of the action potential. Reduction of extracellular Na^+ below a critical level decreases the action potential until it becomes too small to stimulate adjacent areas.

The fact that action potentials can be abolished and then restored by manipulating the electrolyte concentration of the extracellular fluid is evidence that absence of depolarization (electrical silence) and cell death are not necessarily synonymous. Of course, when single muscle fibers are studied, a transmembrane resting potential will be recorded even in the absence of an action potential. Once even the transmembrane resting potential is reduced to or sufficiently near zero, it is likely that the cell is no longer viable. However, the clinical electrocardiogram gives no information in regard to the resting potential, so that the loss of electrical activity as manifested by pathologic Q waves, notched R or S waves, or a decrease in amplitude of R waves may reflect a temporary loss of action potential due to localized alterations in the cell membrane rather than cell death.

Electrocardiograms recorded from patients with electrolyte disturbances es

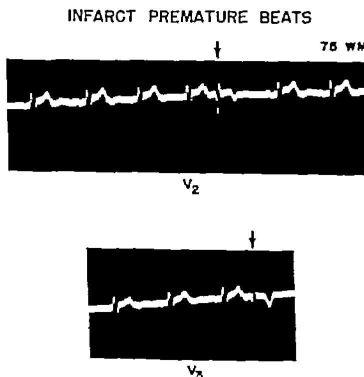
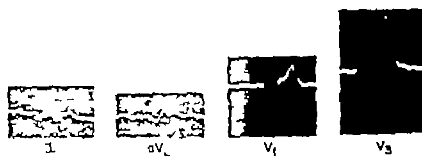


Fig. 7. Leads V_2 and V_3 recorded from a patient with ischemic heart disease. The atrial premature complexes in Lead V_2 and V_3 display pathologic Q waves. The patient died a few hours after the tracing was obtained and at postmortem examination a fresh anteroseptal myocardial infarct was found.

EKG OF PATIENT WITH HYPERKALEMIA



[illegible] patient with terminal renal disease whose [illegible] are present in Leads I and V [illegible] and a [illegible] d V1. This tracing may reflect the loss of [illegible] resting transmembrane potential asso- [illegible] K+. The QS wave in Lead I and the [illegible] the development of silent areas within [illegible] marked decrease in the action poten- [illegible] potentials to activate neighboring myo- [illegible]

pecially hyper[illegible] dem- onstrate in addition to the usual T wave changes, pathologic Q waves in some leads as well as notching and other ab- normalities of the QRS complex. Correc- tion of the electrolyte disturbance is usu- ally associated with disappearance of the pathologic Q waves. It should be stated that the concentration of plasma elec- trolytes may give no indication of local concentrations of electrolytes in ischemic or injured areas of heart muscle. For ex- ample, autolysis of myocardial cells second- ary to infarction may release large con- centrations of potassium ions into the surrounding extracellular fluid which may in turn be associated with a reduction or loss of action potentials from the viable cells in the area of infarction. With cellular recovery, proper ionic concentration gradi- ents are re-established and action potentials return. The entire process may occur with no change in serum electrolytes.

Alterations and phasic variations in elec- trical activity of the heart. Normally, all complexes in a particular lead are of es- sentially the same configuration provided that there is no change in the site of the pacemaker. Of course, minor variations in the form of the various electrocardio- graphic complexes may occur as a result of extracardiac periodic phenomena such as respiration. Under certain circum- stances, there may be marked phasic variation in the magnitude of some part or all of the P-QRS-T complexes, a phe- nomenon known as electrical alternans.

Electrical alternans is a relatively rare electrocardiographic abnormality. Ham- burger and associates[?] found only 1 in- stance of electrical alternans in 10,000 electrocardiograms, and Kalter and Schwartz[24] found 5 instances in an analysis of 8,084 electrocardiograms. Alternation of the T wave is the most common form of alternation, whereas alternation limited to the P wave is extremely rare. Isolated alternation of the QRS complex is rela- tively rare. Total alternans, i.e., simul- taneous alternation of the atrial and ven- tricular deflection, is almost exclusively associated with pericardial effusion and tamponade.[4]

Alternating phenomena from the heart are generally considered to show a 2:1 stimulus-response ratio, i.e., for every two beats there is one alternation. How- ever, for conceptual purposes, any phasic function may be considered to be an ex- ample of electrical alternation. For ex- ample, in Fig. 9, every other QRS com- plex is of less amplitude than the preceding QRS complex. This is the typical ventricular electrical alternans. It

in Fig. 10 there is a progressive decrease followed by a progressive increase in the amplitude of the QRS complex. Such a staircase phenomenon is probably more aptly referred to as periodic rather than as alternating.

The mechanism of alternating electrical phenomena is unknown. In the case of total electrical alternans associated with pericardial effusion and tamponade, the alternans is undoubtedly related in some way to the presence of pericardial disease. It has been amply demonstrated that withdrawal of the first small increment of fluid from the pericardial sac is followed by disappearance of the electrical alternans.[3] In such instances it has been postulated that alternation may have been due to changes in the spatial orientation of cardiac electrical vectors secondary to mechanical factors associated with pericardial effusion and tamponade.

The above-mentioned mechanism does not explain electrical alternans in patients without pericardial effusion. At one time it was considered to be likely that electrical alternans was due to prolongation of the refractory period in some myocardial fibers so that these fibers responded to every alternate beat, i.e., a certain portion of the myocardium was electrically silent during every other electrical systole. As indicated above, prolonged refractoriness was considered to be the mechanism whereby pathologic Q waves developed during episodes of tachycardia or angina pectoris. However, in electrical alternans there is a change in magnitude of the entire QRS complex, but pathologic Q waves do not develop as would be expected if a portion of the myocardium were to become electrically silent with every other sinus impulse.

The most significant arguments against the possibility that prolonged refractoriness is responsible for the production of electrical alternans comes from studies on single muscle fibers. It has been shown by Hoffman and Suckling[29] and by Kleinfeld, Magin, and Stein that electrical alternans can be elicited from single ventricular muscle fibers. Using such a preparation, Kleinfeld and associates[7] described four types of alternation: (1) alternation in the rate of depolarization, (2) alternation in the rate of repolarization, (3) alternation in the magnitude of the action potential, and (4) alternation in the magnitude of hyperpolarization. The demonstration of electrical alternans in single muscle fibers is strong evidence against the hypothesis that electrical alternans is due to refractori-

ELECTRICAL ALTERNANS

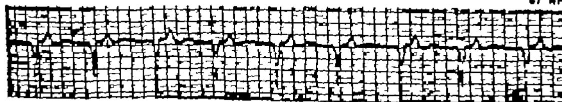


Fig. 9. Ventricular electrical alternans recorded in Lead V... in a patient with a healed anteroseptal myocardial infarct (consult text for details).



Fig. 10. Periodic ... in the amplitude of the R wave recorded in Lead V... in a patient with digitalis intoxication and bigeminy. Note that the R wave in the normally conducted beats (reading from left to right) decreases, then increases ... amplitude. This variation persisted with the same periodicity through ... longer strips and occurred with ... frequency of about 4 cycles per minute, obviously too slow to be attributed to respiration. The phenomenon ... disappeared after withdrawal of digitalis.

ness of a portion of the myocardium to alternate sinus impulses Instead the findings suggest that electrical alternans is due to variations in the rate and magnitude of ionic transfers across the myocardial cell membrane [4] It may be postulated for example that ventricular electrical alternans is due to an alternation in Lx due to some change in the myocardial cell membrane associated with ischemia anoxia or electrolyte disturbance Under these circumstances electrical alternans may be considered to be due to the development of partially but not totally silent areas It must be emphasized however that there are many forms of alternating and periodic electrical phenomena from the heart and although it is generally agreed that such phenomena are usually associated with extensive myocardial disease there is no general agreement on the mechanism of their production It is more than likely that no single hypothesis will explain all types of phasic cardial electrical phenomena

The aging process Certain electrophysiologic changes associated with aging are not readily detected in the clinical electrocardiogram However more sensitive recording equipment has demonstrated changes associated with aging which may be of significance [9] Myocardial infarction is associated with distortion of the QRS sÊ loop of the spatial vectorcardiogram [10,11] The distortion is considered to be due to shortening of the mean instantaneous vectors inscribed during depolarization of the area of infarction Clinicopathologic studies have confirmed the fact that distortion of the QRS sÊ loop is frequently associated with myocardial infarction [10] Another type of distortion of the QRS sÊ loop consists of minor degrees of irregularity of the loop [9] These irregularities or minor distortions are not so definite as the distortions seen with myocardial infarction Previous studies from this laboratory have shown that aging is associated with progressive minor distortion of the QRS sÊ loop of the spatial vectorcardiogram [12] In infants and children the QRS sÊ loops are usually smooth in contour whereas in older age groups varying degrees of distortion of the QRS sÊ loop are relatively frequent The incidence of such distortions increases with age The electrocardiograms from older patients with minor distortion of the QRS sÊ loop may be normal in every respect It should be emphasized that the aging process is associated with only minor degrees of distortion of the QRS sÊ loop which are quite different from the distortion associated with myocardial infarction

The mechanism of the distortions of the QRS sÊ loop associated with aging is unknown It is probable that all distortions of the QRS sÊ loop whether major or minor are abnormal and are associated with loss of electromotive force Autopsy studies in older patients with minor distortion of the QRS sÊ loop frequently show the myocardium to be grossly and histologically normal Thus if the distortions are due to loss of cardiac emf the loss of emf must be secondary to alterations within the myocardium which are not associated with death and scarring of myocardial cells It may be that aging is associated with physicochemical changes within the myocardial cell which render viable cells electrically silent

Summary

The purpose of this paper was to describe some instances in which there may be loss of electromotive force (emf) from myocardial tissue without biologic death of the tissue Myocardial tissue which is electrically inactive although viable is considered to be electrically silent Electrically silent myocardial tissue may under the proper circumstances regain electrical activity The development of areas of electrical silence within the myocardium may be associated with electrocardiographic alterations particularly pathologic Q waves Such Q waves disappear after the area of electrical silence recovers It is important to recognize the fact that loss of cardiac emf is not synonymous with tissue death Judgment concerning the extent of a myocardial infarction or the significance of pathologic Q waves (or other changes in the QRS complex) in patients with tachycardia angina pectoris or electrolyte disturbances should take into consideration the possibility of the presence of electrically silent areas Furthermore awareness of the elec

trocardiographic alterations associated with electrically silent areas of myocardium provides an understanding of some difficult electrocardiographic problems and makes it unnecessary to invoke alterations in rotation position or sequence of depolarization to explain electrocardiographic findings which do not correlate with the autopsy data.

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Diuretic therapy

Part VI. Metabolic complications of thiazide therapy and their correction

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The major complications of thiazide diuretic therapy are hypokalemia, hyperuricemia, hyperglycemia, low salt syndrome, and elevation of blood urea nitrogen.

I. Hypokalemia. The most important unwanted side effect of thiazide therapy is hypokalemic alkalosis. This complication accounts in large part for the serious cardiac arrhythmias in patients on a maintenance dose of digitalis. In general, this can be corrected or prevented by *supplemental potassium, by drugs that block the excretion of potassium, or sometimes by intermittent thiazide therapy.* The use of additional foods that are high in potassium and low in sodium, such as orange juice, raw carrots, and bananas, although of some help, is not adequate for a patient with a strong stimulus to loss of potassium. The average patient cannot be counted on to consume more than 15 to 20 mEq. of extra potassium in this fashion. *A supplement of 40 mEq. a day* or more is usually necessary in the form of potassium salts given orally.

Patients with fluid retention due to portal cirrhosis or nephrotic syndrome or with malignant hypertension secrete large amounts of aldosterone, exchange potassium for sodium avidly, *and are prone to* develop hypokalemic alkalosis even when thiazides are given intermittently. The high rate of secretion of aldosterone in these patients necessarily decreases, by exchanging sodium for potassium, the loss of sodium in the urine, often to the point of blocking diuresis. It is rational to use in these patients an aldosterone antagonist, such as spironolactone, both to conserve potassium and to permit natriuresis. *It is also wise to give supplemental* potassium in many cases.

In the case of chronic congestive failure, hypokalemic alkalosis occurs frequently, but the levels of aldosterone are usually not as high. The patients, when on continuous thiazide therapy, can usually be treated either with supplemental potassium salts or with an aldosterone antagonist. When patients with congestive failure require only occasional thiazides, *potassium supplementation may not be necessary.* However, since most of these patients are on digitalis, and since digitalis toxicity precipitated by hypokalemia can be dangerous, supplemental potassium is usually desirable.

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Patients receiving large doses of thiazides for hypertension who are not rigidly restricted as to the intake of salt show considerable variation in the responsiveness of their exchange mechanism to sodium depletion. Some of these individuals, after an initial loss of potassium, reach a new potassium equilibrium on an ordinary diet. Patients in this group may not need potassium supplementation, especially since they are not usually receiving digitalis. A drop in serum potassium or symptoms of muscle weakness are indications for the addition of potassium salts to the medical treatment.

Oral potassium salts may be given in several ways. Potassium chloride is available as crystals or a granular powder from which solutions may be prepared. Available also are 300 mg. tablets and enteric coated tablets of 300 mg., 500 mg., and 1.0 Gm. The solutions and tablets are inexpensive and effective, but their use is often restricted because of an unpalatable taste and gastric irritation. The enteric-coated tablets may be irregularly absorbed and may even be excreted in the stools. Three grams of potassium chloride contain about 40 mEq. of potassium, which is the normal prophylactic supplement. Eighty to 100 mEq. of potassium a day may be given for the treatment of hypokalemic alkalosis if renal function is adequate. A generally acceptable solution is a mixture of 10 per cent each of the citrate, carbonate, and acetate salts of potassium. A teaspoonful (5 ml.) of the solution contains 15 mEq. of potassium. Three teaspoonfuls a day after meals would usually be an adequate prophylactic dose. Another potassium salt is potassium gluconate. This is usually given as a flavored solution containing 20 mEq. of potassium per tablespoonful or as a tablet containing 5 mEq. of potassium. Two tablespoonfuls of the solution or 8 tablets a day would supply 40 mEq. of potassium. These preparations are well absorbed and somewhat more palatable than potassium chloride.

Several thiazide drugs are prepared in combination with potassium salts, but in general the amount of potassium in such a combination is inadequate. Hydrochlorothiazide is available in 25 mg. tablets with 572 mg. of potassium chloride and 50 mg. tablets with 1,000 mg. of potassium chloride. Bendroflumethiazide is available in tablets of 2.5 and 5.0 mg. in combination with 500 mg. of potassium chloride. Cyclothiazide is available in tablets containing 2 mg. of cyclothiazide and 500 mg. of potassium chloride. Thus, if the maximum effective dose of thiazide given daily is combined with potassium in a tablet, only 2.0 Gm. of potassium chloride would be administered.

II. Hyperuricemia. A second important metabolic complication of the use of thiazides is hyperuricemia. Although it has been suggested that there is a direct effect on uric acid metabolism, it is likely that hyperuricemia induced by thiazide medication is due to interference with renal reabsorption of urate. An elevated serum uric acid under these circumstances usually is not associated with symptoms. Thiazides will occasionally precipitate attacks of clinical gout in gouty individuals, but only a few episodes of gout have been reported in persons in whom there was no prior history of gout. Whether this represents the unmasking of latent gout or its actual production is difficult to ascertain. Uricosuric agents such as probenecid and sulfinpyrazone can completely prevent this secondary hyperuricemia, and although they also block the excretion of thiazides, they neither prolong, increase, nor decrease the diuretic effects. Thus gout is no real contraindication to thiazide therapy. It has been reported by some that correction of potassium depletion will prevent hyperuricemia, but others have been unable to confirm this.

III. Hyperglycemia. Another fairly frequent complication of thiazide therapy is hyperglycemia. The mechanism of this effect is not renal. The hyperglycemia does not appear to be related to a pancreatic effect, since pancreatectomy does not reverse thiazide-induced hyperglycemia in the dog. The actual mechanism of thiazide hyperglycemia is still unknown. The effect is most prominent in diabetic and pre-diabetic patients but has been noted in normal subjects. However, even in diabetic patients the effect is not marked, and standard antidiabetic measures are ordinarily adequate to control the exacerbation of diabetes so produced.

H. *Low salt syndrome.* In disease characterized by the retention of fluid, total body sodium is ordinarily markedly increased so that a true low salt syndrome is difficult to produce. When thiazides are used in patients with hypertension and diabetes insipidus, however, the possibility of inducing a true low salt syndrome in situations in which there is excessive sweating, high environmental temperature, or diarrhea must be considered. The use of replacement sodium chloride is of course specific.

Hyponatremia of the dilutional type is seen in severe congestive failure even without diuretic therapy. Although thiazides reduce the clearance of free water and cause a more concentrated urine, there is no evidence that they produce dilutional hyponatremia any more frequently than do other diuretics. In the treatment of dilutional hyponatremia, the use of sodium chloride is contraindicated.

I. *Elevation of blood urea nitrogen.* Another complication of thiazide therapy is a reduction in the glomerular filtration rate mediated primarily by a fall in cardiac output and plasma volume. In most patients this is of no clinical significance, but in patients with renal insufficiency, with or without hypertension, this effect may cause a marked rise in blood urea nitrogen and renal failure. A progressive rise in blood urea nitrogen occurs rather consistently in patients with initial blood levels above 40 mg. per cent, and thiazides cannot ordinarily be used in these patients.

In the presence of lesser degrees of renal dysfunction, the response to thiazides is unpredictable, and a therapeutic trial with frequent evaluation of the blood urea nitrogen is necessary. A transitory rise or a small rise which then stabilizes at a new level that is 10 to 15 mg. per cent higher is not a contraindication to the continued use of the drug.

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Hemodynamic effects of occlusion of the abdominal aorta during nitrogen mustard therapy

Hames nd a sociates in Nairobi ha e in e t gated the hemod namic effects of occlu ion of the abdominal aorta Th procedure used to protect the pelvic bone marrow during high dosage nitrogen mustard therapy for head nd neck cancer The occlu ions were carried out u ng an inflatable tourniquet or a sandbag and Esmarch tourniquet to compress the abdominal aorta Th procedure i the method of choice in Nairobi for the treatment of head and neck cancer nce no ra or radio therapy is a ailal le The investigation was timu lated by the observation that prolonged hypotensive period occur after removal of the tourniquet

The investigation was carried out on 20 adult African patient w th cancer of the head nd neck The patients were anesthetized w th thiopentone and paralyzed with gallamine triethiodide they were then intubated and entilated w th po ti e pres ure re piration u ing a Radcliffe pump The ri ht side of the heart w catheterized but only one site of measurement of pre ure was used n each individual and w s monitored throughout the procedure The ites at which pre ures were mea ured wer the right trium the pulmonary artery and the pulmonary wedge A comparison of cardiac output before during nd fter the procedure was made in 6 patients by comparing the area nder dy curves written on a Cambridge dye-dilution curv recorder The dy used was azovan blue Endotracheal pre ures were measured in ? patients u ing a water filled tube that conne ted the endotracheal tube to a p essure tran ducer Alteration in the lume of the index fingers were mea ured in 6 patients u ing a w ter filled plethy mogr ph fitted over the finger and connected to a pres ure transducer A decrease the ize of the tra er was taken to indicate inc ease in peripheral esi tance and an increase to indicate fall

The olume of blood box oc lu n u ing manual pres ure over a small sandbag was compared with that u ing an flatable cuff w th azov blue

Four patients were screened before during and after occlu ion and the alteration in cardiac sil houette were noted Blood pres ures and pulse rates were mea ured frequent interval La tly a mall polyethyl ne catheter w introduce l into the femoral arte y and the pres ures were moni tored throu hout the in e tigation —during the or cl rer pres ures were recor led

Atrial pres ures ros during cclu 1 fell to normal levels afterward Pulmonary arterial pres ures rose transiently as the occluding cuff wa being inflated but thereafter returned to normal The wedge pre sure which wa measured in only 1 patient rose during occlusion Femoral arterial pres ures rose during inflation of the cuff when the cuff wa deflated the pres ures were lower than the in tial pre ures but then rose during the next 2 minutes to a level higher than that prior to the procedure

There was a suggestion that the cardiac output fell or remained unchanged during the occlu ion but it rose steeply after the tourniquet was re moved Endotracheal pressures rose slightly during the procedure The changes in olume of the finger were ariable but there was a fall in volume in 4 of 6 patients when the tourniquet wa released There was no ignificant difference in the estima tions of blood olume

Screening during occlu ions showed fir t of all a prominence of the left entricle then the whole heart wung to the right and th was followed by an apparent enlargement of the right atrium and entricle These changes occurred in reverse when the pressure w s released

The frequent fall in cardiac output during oc clusion nd the elevation of pressures in the right heart and wedge pressures were taken to indicate that the heart had temporarily failed this w thought to be supported by the appearance of the heart on screening Because the pulse te d d not alter materially the conclu on was that the troke olum had diminished The reason for this ap pa ent failure was hown not to be due to failure in face of a udden h perten ion ince the blood pres ure d d not change ne ther was it consdered that the sl ght elev tion endotracheal pres ures coul l be incriminated The nitrog n mustard itself could not be a fact ince it w gi en after the d e curves ha l been draw Also the high right trial pres ures indicated that a fall in venous re turn could not be a factor

It was thou ht that two pos ibilities could be considered (1) a failure of mu cle contract lity ociated w th a dimin hed coronary supply and (2) a d minution di ten ibility of the heart Both th se con l tions may h ve been produced by elev t n of the d aphragm combined with a slight I tion of endotracheal pressure This hypothe recei ed some support from the ob ser tion th t a less diffuse pressure on the abdomen such th

produced by manual occlusion over a sandbag caused less elevation of atrial pressure than did the wider spread of pressure produced by the inflatable tourniquet.

The high output after occlusion was thought to be due to the fact that the heart was acting on the optimum part of the Starling curve because of the high right atrial pressure.

It had been shown by other workers[2] that the occlusion is below the renal arteries, which would mean that the volume of blood above the occlusion should be about 70 per cent. In our measurements and those of Duff the volume of blood above the occlusion was approximately 50 per cent, which suggested that venous return from the limbs was obstructed before the aorta was occluded, thus allowing blood to be pumped into the lower half of the body.

The low blood pressure which occurred immediately on release of the tourniquet may have been due to an over-all fall in peripheral resistance—probably mainly below the occlusion. An increase in resistance which was measured in the arms soon compensated for this with a quick rise in systemic pressure. The profound fall which occurred later on may have been due to the release of substances such as histamine in the occluded gut and legs, and indeed in 3 white patients (not included in this study) marked flushing of the skin in the lower half of the body has been noticed after release of the tourniquet.

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Cor pulmonale due to Schistosoma mansoni

It has been claimed that there are about 150 million people all over the world with schistosomiasis. Fortunately, schistosomal cor pulmonale is the least frequently encountered clinical manifestation of the disease. The finding of isolated ova in the lungs is rather frequent, but not so the schistosomal cor pulmonale, since considerable embolization of eggs into the pulmonary arterioles must occur prior to the development of pulmonary obstructive arteriolitis. Ordinarily, the eggs liberated by the Schistosoma mansoni in the mesenteric and colonic vessels get trapped in the liver and do not reach the lungs. In order for enough ova to reach the lungs the presence of portal hypertension with collateral venous circulation is needed so as to allow the direct passage of the eggs through the collaterals into the right side of the heart and from there to the pulmonary arterial tree.

The lesions in the lungs may be produced directly by the ova, may result from an allergic phenomenon in association with the ova and/or its products, or may be secondary to pulmonary arterial hypertension.

When the ova lodge in the pulmonary arterioles an inflammatory process occurs in the wall of the vessels with a granulomatous reaction containing inflammatory cells and occasionally eosinophils. Eventual fragmentation of the elastic lamellae will occur with the formation of pseudoaneurysms which will develop into a dumbbell type of granuloma with an intra-arterial and a para-arterial component. Neoformation of blood vessels known as intra-arterial angiomatoids may occur. The occlusion of vessels by the granulomatous process and pseudoaneurysms is important in leading to pulmonary arterial hypertension and cor pulmonale.

An arteritis characterized by fibrinoid necrosis of the wall and fragmentation of the elastic fibers is frequently encountered. It is considered to be an allergic manifestation as well as the formation of hyalin thrombi. These allergic processes also contribute to the development of pulmonary hypertension.

Once pulmonary hypertension exists, further vascular changes may occur, characterized by diffuse fibroblastic concentric proliferation of the intima with reduction of the lumen of the pulmonary arterioles.

Clinically, the patient complains of dry cough, palpitations, and dyspnea. Some may have precordial pain or discomfort. The final stage is characterized by the classic manifestations of failure of the right side of the heart. Since all these patients have a portal hypertension, they may bleed from esophageal varices and present a history of hematemesis and/or melena. One should strongly suspect schistosomal cor pulmonale in a patient who has a history of melena or hematemesis with pulmonary hypertension.

Physical examination shows a parasternal heave and an accentuated second pulmonary sound. A systolic murmur in the second or third intercostal space along the sternal line is frequent. A diastolic murmur of pulmonary regurgitation may be present. Auscultation of the lungs is characterized by the absence of abnormal findings. Hepatosplenomegaly is almost always present, since the development of the cor pulmonale depends upon the presence of

the portal hypertension Cyanosis and clubbing occur in a small number of cases the former being more frequent in cases with heart failure In some instances the presence of arteriovenous communication may cause cyanosis[11]

X ray films show that the pulmonary artery and its main branches are increased and the peripheral lung fields may be relatively anemic In some instances the pulmonary artery reaches aneurysmal size The enlarged right ventricle is easily recognized on roentgenologic study The electrocardiogram reveals right ventricular hypertrophy and prominent P waves compatible with enlargement of the right atrium Cardiac catheterization confirms pulmonary hypertension with increased pulmonary vascular resistance and normal pulmonary capillary pressure [7,11] Cardiac output at rest is normal unless failure of the right side of the heart supervenes Smears of peripheral blood may show eosinophilia

There are certain clinical findings which whenever present make the diagnosis of schistosomal cor pulmonale almost sure A patient is considered to have schistosomal cor pulmonale as the underlying disease until proved otherwise when he has been exposed to an endemic area and is found to have schistosomal ova in the stool or by rectal biopsy and when he develops pulmonary hypertension in association with hepatosplenomegaly with portal hypertension and esophageal varices and has associated eosinophilia

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The examination of urine

Recent work has revealed the prevalence of unsuspected and asymptomatic infection of the urinary tract That this associated with acute and chronic pyelonephritis is well established [1] There is also some evidence to suggest that asymptomatic bacilluria is associated with arterial hypertension although an etiological relationship is more difficult to prove

Methods for the diagnosis of infection of the urinary tract have become more clearly defined over the past 10 years It has been demonstrated that it is no longer justifiable to catheterize the bladder to obtain specimens of urine for analysis Several techniques for the collection of clean specimens of urine without the use of catheters have been described All suffer from the disadvantage that some contamination of the specimen of urine is inevitable

In many laboratories it is still the routine practice to leave urinalyses to the most junior and often most overworked member of the staff After a variable delay an unmeasured quantity of urine is placed on each of two or three culture media any growth is recorded and the organism is identified Moreover it is often the practice not to culture the urine unless a certain number of white cells are seen in the urinary deposit

Such method cannot possibly distinguish between contamination and infection of the urine Some form of quantitation of the bacterial content of the urine has been advocated to enable one to make the [illegible] infection The urine is an excell

culture medium for the less fastidious organisms usually associated with infection of the urinary tract. Bacteria originating within the urinary tract will therefore multiply in the bladder and reach a high concentration per milliliter of urine before the urine is voided. On the other hand, organisms which accidentally enter the urine during collection will be present initially in small numbers. If the urine is cultured immediately or stored at 4° C. until the culture can be carried out, this difference in concentration of organisms can be utilized to show if the urine is truly infected.

Many methods of quantitation have been described. Personal preference is for a pour plate culture in which 1 milliliter of each of a 1:100 and 1:1000 dilution of urine is flooded with cooled melted agar and incubated for 24 to 48 hours.

Criteria of what constitutes true infection for this method have been well established. It is clear that in the majority of occasions, if the infection originates within the urinary tract, more than 100,000 organisms per milliliter of urine will be found. Conversely, contaminants will rarely be present in concentrations greater than 10,000 per milliliter. The statistical limits of these criteria must be established for each laboratory. Kass[1] has tested his confidence limits using a midstream collection and a pour plate culture method as follows: If the first culture contains more than 100,000 organisms per milliliter, then a second culture will confirm this finding on 80 per cent of occasions. If the first culture shows less than 10,000 organisms per milliliter, repeat culture will reveal bacilluria in less than 1 per cent. Fewer than 5 per cent of cultures count in between 10,000 and 100,000 organisms per milliliter, and these must be repeated.

In our own experience, using methods similar to those of Kass, these confidence limits have been attained. It must be pointed out that these criteria are invalidated if (1) the urine is left at room temperature for longer than 3 hours before culture or refrigeration, (2) there is a high flow of urine and insufficient time is given for the organisms to multiply in the bladder, and (3) a highly acid urine is present. (4) If the patient is receiving antibacterial therapy, many kinds of organisms (unless highly resistant) will not multiply in the presence of the concentration of these drugs found in the urine. Contaminating organisms will be exposed to the drug for a shorter time and might be expected to grow occasionally on the culture plate. (5) Some organisms, e.g., *Streptococcus faecalis*, do not multiply readily in the urine.

The routine methods for examining the urinary deposit have also been shown to be misleading. It has been shown that in 55 of 142 urines examined in which 1 to 5 cells were seen per high power field, the urinary white cell excretion rate was above 400,000 per hour, and among 67 normal subjects the white cell excretion rate exceeded 400,000 per hour in only 2. Moreover, bacilluria may be found even in the presence of a normal cell excretion rate.

Thus the routine examination of a specimen of urine should include (1) careful technique of collection, (2) some form of quantitation in examining for formed elements, and (3) a quantitative culture.

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Is histamine the "trigger mechanism" of endotoxin shock?

It has been noted that regional vascular effects induced by endotoxin develop only if the organ is perfused with blood and do not occur when plasma, dextran, or gelatin are substituted for whole blood or when the regional circulation is totally isolated from the animal with a mechanical pump-lung. This has prompted a search for substances which mediate the early vascular responses to endotoxin. Recently, Hinshaw and his collaborators have proposed an attractive hypothesis to account for the initial hemodynamic events induced by endotoxin. According to their concept, the injection of endotoxin in the dog is followed by a massive release of histamine from blood and tissues which cause portal venous constriction, splanchnic pooling, and a decrease in venous return to the heart, cardiac

output then declines and hypotension ensues abruptly with a subsequent release of catecholamines.[7] This sequence constitutes the early phase of endotoxemia in the dog and histamine might be termed the "trigger mechanism" of endotoxin shock.

Several lines of evidence have been advanced by Hinshaw to support the primacy of histamine as the mediator of the initial vascular responses to endotoxin[7] (a) There are many common vascular responses which can be elicited either by endotoxin or histamine (b) During endotoxemia circulating concentrations of histamine increase ( ) Vascular reactivity to histamine is enhanced after the administration of endotoxin (d) Pharmacologic antagonists of vascular responses to histamine also antagonize vascular responses to endotoxin ( ) Pretreatment of animals with drugs which release histamine from tissue modifies subsequent vascular responses to endotoxin In addition the advocacy of an important role for histamine early in endotoxemia draws some support from other work which has implicated histamine in the late stages of endotoxin shock and other forms of vascular collapse.

There is however strong evidence against the proposition that histamine is the primary mediator of the initial stage of endotoxin shock. First histamine is not unique among naturally occurring vasoactive substances in its ability to induce hemodynamic changes which mimic events occurring early in endotoxemia. Thus epinephrine like endotoxin can induce shock, a delayed fall in total peripheral resistance,[11] splanchnic pooling and hepatic venoconstriction. Similarly acetylcholine like either histamine or endotoxin has been shown to decrease systemic arterial pressure, increase portal pressure and decrease resistance across the perfused limb. Vasoactive polypeptides released in endotoxemia also decrease systemic arterial pressure. Furthermore there are at least three early vascular responses to endotoxin which do not result from the administration of histamine namely the maintenance of total peripheral resistance for the first 10 to 30 minutes after endotoxin,[19] certain circulatory responses of the isolated lung to endotoxin and the abrupt rise in mesenteric arterial pressure in the perfused stomach preparation.

The increase in circulating concentration of histamine after injection of endotoxin has not been observed in all reports. Thus Hinshaw and his collaborators have reported both an increase and a decrease in the concentrations of histamine in peripheral blood. Weil and Spink[20] found no increase in the histamine in peripheral blood but did find an increase in the levels of histamine in hepatic venous blood which was maximal at 1 minute and had disappeared by 5 minutes after endotoxin. In our laboratory we have been unable to find an increase in the concentrations of histamine in either the femoral arterial or portal venous plasma of dogs for up to 5 hours after endotoxin (including measurement obtained at 1, 1 2 and 5 minutes after endotoxin). It may be possible to account for these differences between Hinshaw's findings and our own by the fact that the dose of endotoxin employed by Hinshaw's group was many times larger than our own (an LD_{90}). Furthermore according to one report killed cells were injected.[10] The use of massive doses of such material (probably containing protein) may indeed prompt a rise in circulating histamine but this would not be a response to endotoxin per se. A second point which may explain these differences relates to the method employed by Hinshaw and associates to measure histamine. They reported histamine values as blood concentration, which may account for the frequently variable or high control concentrations observed. It seems to us that histamine bound to formed elements of blood is not the vasoactive substance with which we are concerned and measurements of circulating histamine should be confined to the free histamine in plasma.

Vascular responsiveness to histamine has been reported to be exaggerated during endotoxemia.[9] However examination of reports which describe this finding shows that in dogs the enhanced responsiveness is a late finding whereas within the first 10 minutes after endotoxin (when the "trigger" must be fired) systemic and portal venous responses to histamine are markedly inhibited. In rats and rabbits hyperreactivity to histamine has not been observed.[20] It should also be noted that so-called "induced histamine" activity (as measured by histidine decarboxylase activity) is not elevated early in endotoxemia.

Hinshaw has found that phenoxybenzamine blocks the portal hypertensive response to endotoxin or to histamine. Other reports have also noted this finding[20] and the amelioration of the abrupt arterial hypotension and other vascular responses to endotoxin in dogs administered phenoxybenzamine.[22,24] However phenoxybenzamine is better known for its adrenolytic than its antihistaminic properties. Furthermore phentolamine which has no antihistaminic properties but is an effective adrenergic end organ antagonist also blocks vascular responses to endotoxin.[24] Finally systemic arterial and portal venous responses to histamine can be blocked effectively with large doses of diphenhydramine, promethazine or pyrilamine, yet these antihistaminics fail to block the same vascular responses to endotoxin.[24] Some amelioration of effects due to massive amounts of endotoxin however has been reported after pretreatment with promethazine.

Hinshaw and associates have reported that pretreatment of dogs with a histamine releasing agent (Compound 48/80) alters subsequent vascular responses to endotoxin. We have not confirmed this nor have we found that reserpine (which also reduces tissue stores of histamine) materially modifies the major hemodynamic events of endotoxemia.[24] Similarly it has been found in rats that Compound 48/80 does not alter mesenteric vascular reactions induced by endotoxin.[24]

There is other evidence against the histaminic trigger mechanism relating to species differences. Hinshaw and associates have noted that immature dogs do not exhibit the abrupt arterial hypotensive response to endotoxin whereas an abrupt fall in pressure is seen in puppies during systemic release of histamine. Similar responses occur in the monkey. The lethal dose of endotoxin is approxi-

Book reviews

HOW TO PRODUCE A READABLE ELECTROCARDIOGRAM. By Bertram A. Bradlow, M.D., Johannesburg Hospital, Johannesburg, South Africa. Springfield, Ill., 1964, Charles C Thomas. 187 pages. Price $8.50.

This is a nontechnical treatise aimed at the clinical and hospital cardiologist who uses a single-channel, direct-writing electrocardiographic recorder. It is full of common-sense advice about recognizing and correcting errors and artifacts in the electrocardiogram. It should be recommended reading for the physician, nurse, or technician who has the responsibility for taking electrocardiograms. No knowledge of electronics is required to understand the book.

The physician who takes portable electrocardiograms will welcome some real solutions to such problems as how to carry the instrument in the car, how to handle the problem of the A.C. power line cable, and what to do when the paper runs out.

The author has given the reader much useful information on how to judge the performance of an electrocardiographic machine by noting aberrations in the standardization pulse. Since most readers will not be likely to have audio generators to determine the frequency response characteristic of their own instrument, this is a commendable approach.

There is a full section on how to carry out the exercise tests, including some practical suggestions for simplifying the standard number of ascents for patients of different weights and ages. There is also an excellent section on labeling, mounting, and filing the finished electrocardiogram for the small clinic or office. The book does not cover the more complex mounting and filing problems of the large hospital and therefore does not discuss the new techniques of microfilming nor the newer rapid-search filing and reproduction techniques used by these institutions.

The illustrations are clear, readable, and well labeled. There is evidence of excessive and often unnecessary retouching of the tracings, but in no instance does this detract from the point being made.

The appendix is brief but gives a simple practical method for determining which wire is broken in a three-lead cable without the use of test instruments. Data on the actual skin resistance measurement using various electrode pastes would have been most welcome in the appendix. The author's method of evaluating skin resistance by noting changes in the tracing itself leaves something to be desired.

There are always errors in a new book, and this one is no exception. In the first chapter this reviewer was surprised to learn that the electrical fields produced by the heart are derived from "currents evolved by the contraction of heart muscle." Fortunately, the author has not gone into detail, and the statement appears only once. It is apparent from later statements by the author that this was an editorial slip which can be altered in future printings. Another error noted only in the first chapter is the use of the terms *voltage* and *current* as if they were synonymous; thus the author refers to "a millivolt of current."

This book covers fully matters usually considered on only a few pages in most electrocardiographic texts. The need for better, readable electrocardiograms is so great that this reviewer can only applaud any effort in this direction.

A HISTORY OF ELECTROCARDIOGRAPHY. By George E. Burch, M.D., Henderson Professor and Chairman, Department of Medicine, Tulane University School of Medicine, and Nicholas P. DePasquale, M.D., Assistant Professor of Medicine, Department of Medicine, Tulane University School of Medicine, New Orleans, La. Chicago, 1964, Year Book Medical Publishers, Inc. 309 pages. Price $10.

This remarkable book provides a penetrating excursion through the pages of electrocardiographic history. It represents a contribution which is sound in conception, uniquely succinct yet comprehensive in presentation, and carefully perceptive in its conclusions and interpretations. The reader is provided with a sagacious view of scientific thought which is cleverly interwoven with personal glimpses of the investigators responsible for the growth and development of electrocardiography to a major clinical science. The portrayal is a dynamic one, and the important forces in the history of electrocardiography are carefully identified and evaluated.

The book is divided into eleven chapters. Chapter I, the introduction, sets the tone and reference frame for the presentation and serves to define the place of electrocardiography in the past, the present, and the future. Chapter II carefully traces the development of the electrocardiograph, starting with the discovery of the electromotive activity in living tissue, carrying on through the early instruments used in measuring the electromotive forces of the heart, the first electrocardiograms, the development of the capillary electrometer, and ultimately on to the modern electrocardiograph. Chapter III reviews the lives of the great men of electrocardiography, including such notables as Galvani, Einthoven, Lippmann, Mackenzie, Waller, Herrick, Wenckebach, Hering, Cohn, Lewis, Fahr, Pardee, Wilson, Mann, and several others who perhaps are less well known to the average reader but still of great importance because of their fundamental contribution. Full discu ions of contemporary investigators are omitted, since their places in the history of electrocardiography, although ured, are less well defined at the moment.

The following chapters outline more specifically the development of electrocardiography through time periods influenced by the prevailing methodology or the dominating interests of the particular era. Chapter IV deals with the period of the

capillary electrometer (1877 1901) Chapter V the period of Einthoven and the development of the string galvanometer (1900 1913) Chapter VI the period of the electrocardiographic study of disorders of the heartbeat (1909 1920) Chapter VII the period of study of nonarrhythmic electrocardiographic abnormalities (1915 1937) and Chapter VIII the period of the introduction of the unipolar precordial lead

Chapter IX interestingly and informatively reviews selected aspects of the development of electrocardiographic theory including those on the nature of the cardiac potentials the source of the cardiac potentials and the relationship between electromotive forces of the heart and complexes of the standard limb lead Chapter X traces the development of fetal electrocardiography Chapter XI reviews miscellaneous applications of the Einthoven string galvanometer concluding with views on the uses of the electrocardiogram to monitor the heartbeat of man in space flight

A short appendix is provided which offers a clear and succinct step-by-step chronologic summary of most of the developments important to electrocardiography

The factual data in the book and the important events during the development of electrocardiography are carefully documented in the bibliography This is arranged chronologically so that the reader may readily find the reference which documents any particular point the text I addition to its value in providing documentation for the text this thoughtfully chosen bibliography offers a compilation of the classics in electrocardiography

The paper and printing of the text are of good quality and the indexing more than adequate The book is profusely illustrated showing pictures of men their equipment and the record that both have provided Much of electrocardiographic history can be told through these pictures

This book should be read by all cardiologists and all others with more than just a passing interest in electrocardiography The reader will be justly rewarded

NIACIN IN VASCULAR DISORDERS AND HYPERLIPEMIA Edited by Rudolf Altschul Springfield Ill 1964 Charles C Thomas Publisher 306 pages Price $11

This monograph concerns itself with nicotinic acid and its myriad facets in relationship to cardiovascular disorders The editor commences with a general discussion and covers the gamut from historical to clinical information about niacin this includes the pharmacologic biochemical and therapeutic effects of the drug The theories in regard to the pathogenesis of atherosclerosis are described and each of them analyzed The various mechanisms of action of nicotinic acid along with the side effects and toxicity of the drug are presented and analyzed The resultant conclusion as to the most plausible thesis is that which relates nicotinic acid to the augmentation of DPN and an enhanced oxygenation of blood

After this composite picture of niacin various aspects are studied in detail by several contributors These include the effects on carbohydrate metabolism and especially in regard to glucose tolerance Concerning the effects of niacin on the cardiovascular system several parameters were studied viz cardiac output peripheral resistance pulmonary vasculature and pulmonary function In the use of niacin reports are given on studies of coronary artery disease as evidenced by Heberden's angina electrical conduction defects and myocardial infarction Mention is made of the use of nicotinic acid in renal disease such as glomerulonephritis The therapeutic effects of niacin in disordered metabolism of lipid which includes hyperlipemia and hypercholesterolemia are presented Various theories on the pathogenesis of these diseases and the mode of action of the drug are noted In one study arteriograms of peripheral vessels involved with atheromatous changes (exclusive of chronic calcified lesions) before and after treatment with nicotinic acid are displayed These studies show marked improvement in the radiologic picture after therapy Finally studies on the effect of niacin on liver function are evaluated

All in all this monograph covers all aspects of the various studies concerning nicotinic acid It is richly endowed with comprehensive references and should prove to be invaluable to the clinician researcher biochemist or student interested in the problems concerned

GIVE AND TAKE THE DEVELOPMENT OF TISSUE TRANSPLANTATION By Francis D Moore M D Philadelphia 1964 W B Saunders Company 182 pages Price $3 50

This brief summary of the history of the development of tissue transplantation As would be expected there is no new idea in the book It is a documented presentation of some of the more important steps in the history of tissue transplantation The major portion of this small book devoted to transplantation of the kidney when the greatest experience has been with the skin Why the skin is neglected in discussions of this sort or as model for studying the immunologic problem great mystery The skin has been used for decades to measure sensitivity to drugs allergens chemical physical factors and the like The skin readily available for direct observation and use in the study of the many problems involved but the author of this book as do others ignores these facts However this book should be of interest to those working with organ transplantation

Announcements

SECOND NATIONAL CONFERENCE ON CARDIOVASCULAR DISEASES. For more than a year 400 scientists have been working in committees summarizing the progress of knowledge, the needs and special opportunities for research in the field of heart and blood vessel disease including physiology, epidemiology, genetics, congenital heart disease, pharmacology, pathology, radiology, infectious bacterial endocarditis, pericarditis, myocarditis, rheumatic fever, rheumatic heart disease, cerebral, peripheral and pulmonary vascular disease, hypertension, arteriosclerosis, traumatic heart disease, psychogenic factors in cardiovascular disease, myocardial failure and cardiac arrest, cardiovascular surgery, thromboembolic disorders, stroke, chronic care, rehabilitation, the effects of aging, artificial organs and devices to assist the circulation, lay and professional education, and community services. These scientists with 200 more invited experts in research, treatment, education and community services will meet November 22 through 24, 1964, in Washington, D. C., in the Second National Conference on Cardiovascular Disease to review and discuss these detailed summaries and interpretations of developments in the cardiovascular field since the First National Conference in 1950.

Additional objectives of the Conference are (1) to examine the cost of cardiovascular diseases in terms of their burden on human, financial and social resources; (2) to improve and implement the application of new knowledge at the community level; and (3) to assist physicians, other health personnel, and the public in useful and wider application of current knowledge through publications and dissemination of the results of the Conference.

The Conference is being sponsored by the American Heart Association, the National Heart Institute and the Heart Disease Control Program of the United States Public Health Service.

Originally scheduled for January 1965, the meeting has been moved forward to Nov. 22-24, 1964, in order to facilitate the most fruitful possible exchange between the Conference and the President's Commission on Heart Disease, Cancer and Stroke, which must submit its report in December.

SYMPOSIUM ON OXYGEN, the Sixth International Basic Science Symposium of the New York Heart Association, will be held in New York City at the Biltmore Hotel Friday and Saturday, Dec. 4 and 5, 1964.

For information on registration write to Alfred P. Fishman, M.D., Symposium Chairman, New York Heart Association, 10 Columbus Circle, New York 19, N. Y.

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Acknowledgment to reviewers

The Editors wish to express their thanks and appreciation to the following who have aided in the review of manuscripts during the past year.

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The value of converting atrial fibrillation to normal sinus rhythm

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With the advent of a new method for converting arrhythmias to sinus mechanism, namely, external cardiac electrical shock,[1] it appears pertinent to re-examine the value of restoration of the normal electrical sequence to the heart in the case of atrial fibrillation, since the latter is the most common chronic arrhythmia.

The hemodynamic abnormalities imposed on the circulation by atrial fibrillation are of sufficient magnitude to support the contention that this arrhythmia in and of itself is disadvantageous to the circulation. This disadvantage extends further than a lack of the mechanical shortening of atrial fibers that comes with atrial contraction, since it is well accepted that atrial systole is needed to preserve the competency of closure of the atrioventricular valves.[2-11] It also may contribute a physiologically important volume to the nearly full ventricle in such a way as to set the final level of muscular tone just before ventricular contraction, and hence be a vital regulator of stroke volume.[2-10] Tricuspid and mitral insufficiency appear with atrial fibrillation, and again a forward volume may be lost because of this. Consequent to valvular insufficiency there is sequestration of blood into, and thus congestion of, splanchnic and renal beds which may be detrimental.[11] Poor emptying of the atria and the sludging of blood in these relatively passive pools favors the formation of clots, which is known to be a common complication of this rhythm. Finally, an over-all decrease in cardiac output follows the onset of atrial fibrillation. And this may compromise blood flow to such vital areas as the brain, kidneys, liver, and bone marrow, as well as to the muscular system. Thus, symptoms not only of general body fatigue, either at rest or on exertion, but also of giddiness and change in memory, as well as more serious disorders of the nervous system, may ensue. Less symptomatic but equally fundamental dysfunctions such as retention of sodium or nitrogen and altered liver functions are also likely.

In our experience, conversion to sinus rhythm in patients who are in congestive heart failure may actually be the turning point in a situation which appeared to represent an irreversible stage of heart failure. This has been reiterated recently by Freeman and associates.[1] The improved

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exercise response of such patients after conversion has also been demonstrated.[11,13,14]

In view of the deleterious effects of atrial fibrillation and the well-recognized increased difficulty of its reversion during the early postoperative period after pulmonary, pericardial, or cardiac surgery, it appears reasonable to urge the prophylactic use of quinidine (or procaine amide) in all patients who are likely to develop atrial fibrillation after thoracic (cardiac or pulmonary) surgery. In our hands this prophylactic program has been highly successful in preventing the arrhythmia. Quinidine should be started at about the sixth to eighth postoperative hours unless blood pressure is low or falling. The intramuscular preparation (quinidine sulfate in propylene glycol) should be used for the first few days until the patient is eating well; the oral drug can then be substituted.

There are, of course, certain patients in whom conversion may be difficult or impossible or in whom maintenance of sinus rhythm cannot be accomplished. These are most likely to be those in whom the atria are greatly enlarged or those in whom the myocardium is the site of recent and/or extensive inflammation due either to the basic disease process, to postoperative pericarditis, to suture material after operation, or to widespread chronic fibrosis.

Recognizing, therefore, that there are instances in which it is difficult to achieve and maintain conversion, one may ask what are the dangers of conversion and how much weight should these carry in the making of a decision for or against correction of atrial fibrillation. The disagreeable complications of the drugs utilized to attempt restoration of sinus rhythm are well known. Those attributed to quinidine and procaine amide have attracted more attention than those associated with the digitalis family, and yet the former medications can be monitored and untoward effects prevented with greater precision by utilizing moderate prolongation of the Q-T interval as an index of adequate dosage and its excessive prolongation along with accompanying moderate widening of the QRS complex, lowering of blood pressure, or ventricular irritability as toxic signs. According to a recent report[8] there are no serious or even modest side effects from the newer electric shock therapy carried out under light anesthesia, and in some instances it has even been possible to use the D.C. defibrillator without any general anesthesia and with very little discomfort to the recipient.[4]*

The danger most feared in relation to conversion of atrial fibrillation is, of course, the loosing of emboli into the circulation. At the present time the classic explanation of the phenomenon, namely, the shaking off of particles from the endocardium by the mechanical jarring consequent to resumption of sinus rhythm and hence resumption of atrial systole with increased velocity of flow, is satisfactory for an immediate embolization. Those embolic accidents which occur hours or even days after conversion are best accounted for by the fact that atrial systole with its fractionate contraction of the fibers may require some time to work the particles loose or dislodge a clot on a pedicle. It may also be that atrial fibrillation has returned and then again subsided without being detected. The use of long-term electrocardiographic monitoring devices which operate 24 hours a day may help to solve this problem. It is also possible that there is a hemodynamic explanation for this embolic complication of conversion, but there is little information concerning the adjustments during and immediately after resumption of sinus rhythm. The great bulk of physiologic data in man has been acquired *after sinus rhythm has been restored* for some period of time. The hemodynamic studies being done at present on patients immediately before and after electrical cardioversion† are therefore of considerable importance in this respect.

In summary, there appears to be sufficient reason from a number of aspects to urge reversion of atrial fibrillation to sinus rhythm in almost all circumstances. Maintenance of or reversion to the normal rhythm is warranted, and the difficult facets of maintenance therapy deserve further study.

*The original experience [illegible] has been expanded to include [illegible] (Dr. B. [illegible] and Stock, P. [illegible])

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Clinical communications

Congenital absence of the pulmonary valve

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Congenital pulmonary incompetence due to absence of, or rudimentary, pulmonary valve cusps was practically unknown until a decade ago, although Chevers had briefly discussed two instances of this anomaly as far back as 1847 and Kurtz, Sprague, and White had described a case in 1927. To our knowledge, 33 instances of this anomaly in which the diagnosis had been confirmed at autopsy or operation had been hitherto reported.[1-4] The absence of pulmonary valves is usually associated with a ventricular septal defect and often with infundibular pulmonary stenosis as well. The three lesions together form a distinctive combination. Miller, Paul, and Lev[1] have recently reviewed the clinical, radiologic, and hemodynamic features of this entity. They drew attention to the structural changes in the pulmonary trunk and pulmonary valve region, which were studied histologically in 2 of their cases.

The majority of reported cases of absence of the pulmonary valves were in older children and adults. The clinical manifestations in these differed in some important respects from those in infants. We believe it to be worth while to report the clinical and autopsy findings in 5 additional infants with absence of the pulmonary valves.

All 5 infants had ventricular septal defects. Three of them could be classified as having tetralogy of Fallot with absence of the pulmonary valves, since they had definite infundibular pulmonary stenosis and aortic overriding. In a fourth infant the presence of overriding of the aorta and of infundibular stenosis was borderline. The fifth infant had double outlet right ventricle, a severe form of common atrioventricular canal, an abnormal communication of the posterior aortic sinus of Valsalva with the right ventricle, and a single coronary artery, in addition to absence of the pulmonary valve. All 5 cases were studied by angiocardiography, and 3 of them by catheterization of the right side of the heart.

Case reports

CASE 1. L. B. This female infant was first admitted to the Cook County Children's Hospital on July 27, 1954, at 1 month of age, with a history of cyanosis, respiratory distress, and failure to gain

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weight since birth. On examination she was found to be in severe respiratory distress and was obviously cyanotic. A Grade 4/6 systolic murmur was heard best at the pulmonary area and a Grade 3/6 diastolic murmur at the lower left sternal edge. Râles were present at both lung bases. The liver was not enlarged. X-ray examination of the chest showed a slightly enlarged heart with elevated apex, a prominent pulmonary artery segment and a prominent right pulmonary artery at the right hilum. The right lower lobe appeared to be collapsed and repeat films 2 weeks later showed it to have re-expanded. The ECG indicated definite right ventricular hypertrophy (Fig. 7).

Catheterization of the right side of the heart revealed right ventricular hypertension and a large left-to-right shunt at the ventricular level. The pulmonary artery was not entered. A venous angiocardiogram showed early opacification of the aorta with a right aortic arch and marked dilatation of the pulmonary trunk and its right branch. Reopacification of the right ventricle and pulmonary artery consistent with a left-to-right shunt was present.

She was discharged on a maintenance dose of digitalis and readmitted 2 weeks later with otitis media, which was treated with penicillin. She continued to be dyspneic and cyanotic. Her signs of cardiac failure gradually progressed and she died at the age of 3 [illegible] months.

AUTOPSY CARDIAC FINDINGS. The apex was pointing toward the left; the heart was of triangular shape with the apex formed by the right ventricle. The superior and inferior venae cavae and the coronary sinus entered the right atrium. The foramen ovale was closed. The wall of the right ventricle measured 4 to 6 mm. in thickness. There was a gradual narrowing of the infundibulum terminating in a pulmonary orifice that was only 1.8 cm. in circumference. No pulmonary cusps were present (Fig. 1, A); at the level of the orifice there was only a linear transverse circumferential slightly elevated ridge that was 1.5 mm. in width and several tiny knobby elevations. The supravalvular portion of the pulmonary trunk, which was markedly dilated, measured 1.3 cm. in its external diameter. The pulmonary veins entered the left atrium. The wall of the left ventricle measured an average of 4.5 mm. in thickness. The aortic orifice measured 2.1 cm. in circumference and was overriding a slit-like interventricular septal defect which was located immediately subjacent to the [illegible] ring. There were three semilunar cusps all equal in size with normal origins of the coronary arteries. The aortic arch was right sided with mirror image sequence of origin of the brachiocephalic arteries. The ductus arteriosus was obliterated. *The autopsy diagnosis* was: (1) absence of pulmonary valve cusps, (2) tetralogy of Fallot, (3) marked dilatation of pulmonary trunk, and (4) right aortic arch.

Case [illegible]. F. A. This male infant was the product of a normal pregnancy and [illegible] delivery. He weighed 8 pounds at birth. Cyanosis, respiratory distress, and a loud continuous murmur were noted immediately after birth, and digitalization was carried out on the first day of life. He was first seen at Cook County Children's Hospital on Sept. 18, 1955, at the age of 10 weeks. On examination he was cyanotic and dyspneic and weighed no more than at birth. A loud systolic murmur was heard at the left sternal edge and a low pitched diastolic murmur was heard best at the fourth left intercostal space. X-ray examination of the chest revealed a moderately enlarged heart with an elevated apex, a prominent pulmonary artery segment on the left border, and a very broad right pulmonary artery shadow in the right hilar region. Mediastinal shift to the left due to obstructive emphysema of the right lung was presumably a consequence of bronchial compression by the dilated right pulmonary artery. The ECG indicated right atrial and right ventricular hypertrophy (Fig. [illegible]). A venous angiocardiogram demonstrated early opacification of the aorta, a right aortic arch, and huge dilatation of the pulmonary trunk and its main branches.

He was discharged and subsequently readmitted three times in cardiac failure with râles and rhonchi present all over both lungs. During his final admission at the age of 6 months he developed a temperature of 10[illegible]° F. Two days later the dyspnea suddenly increased and no breath sounds were heard over the right hemithorax. He died a few hours later.

AUTOPSY CARDIAC FINDINGS. The apex of the heart was pointing toward the left; it was formed by the right ventricle. The superior and inferior venae cavae and the coronary sinus entered the right atrium, which was dilated. The valve of the inferior vena cava was prominent; several small thread-like fibrous strands connected it with the crista supraterminalis. The foramen ovale was patent; stretched, it measured 6 by 8 mm. Several smaller fenestrations were present in the septum secundum. There were multiple small nodular excrescences along the free margins of the tricuspid leaflet. The right ventricle was large, dilated, and thick walled, measuring 4 to 9 mm. in thickness. The endocardium of this ventricle was thickened, especially in the outflow tract. The pulmonary orifice measured [illegible]0 cm. in circumference; no pulmonary cusps were present (Fig. 1, B); there was only a [illegible] flattened irregular ridge 2.5 mm. in width along the valve ring. There was sac-like dilatation of the supravalvular portion of the pulmonary artery and marked dilatation of the pulmonary artery branches. At its bifurcation the trunk measured 3.1 cm. in circumference. All pulmonary veins entered the left atrium, which was very small. The wall of the left ventricle measured [illegible] mm. in thickness. The circumference of the aortic orifice measured [illegible] cm. Three cusps were present. The right aortic cusp formed the right margin of an interventricular septal defect which was located just inferior to this cusp; the base of this cusp was [illegible] with the outflow tract of the right ventricle attached to the muscular wall posterior to the parietal part of the crista supraventricularis. The defect measured approximately 5 mm. in diameter. The coronary arteries took normal origins. The aortic arch coursed over the right bronchus, giving origin successively to the left innominate artery, right common carotid artery, and right subclavian artery. No ductus arteriosus was present. *The autopsy diagnosis* was: (1) absence of pulmonary valve cusps, (2) tetralogy of Fallot, (3) marked dilatation of the pulmonary trunk, (4) right

aortic arch (5) absence of ductus arteriosus (6) wide patency of for men ovale (7) endocardial sclerosis of the right entricle and (8) rudimentary Chiari network

Case 3 1 C This infant was adm tted to Cook County Children s Hospital on Aug 14 1962 at the age of 4 d s H had been born normally at full term (weight at birth 6 pounds and 12 ounces) However respiratory di tress and hepatomegaly had been observed immediatel after birth and d g talizat n had been arried out on the day of birth Examination on admission revealed evident cyanosis which increased on crying The respiratory rate was 50 per minute The lungs were normal to auscultation The liver was not enlarged The periph eral pul es were normal A systolic as well as a diastolic thrill were present all over the precordium best felt at the pulmonary area The first heart sound was normal The second sound was inaudible at the base but a ngle second ound was heard at the lower left parasternal area A faint ejection click was heard at the same area A Grade 4/6 long ejec



Fig 1 Pulmonary val e region in Case 1 (A) Case 2 (B) Case 3 (C) and Case 4 (D)



Fig 2 Case 3 Ventricular septal defect seen from left ventricular aspect

tion systolic murmur and a Grade 3/6 early diastolic murmur were both best heard at the pulmonary area These two murmurs had a to-and fro rhythm and were separated by a definite interval The heart rate was regular 60 per minute the ECG showed nodal rhythm Th was thought to be due to digitalis overdosage No further digitalis was given and 2 days later normal sinus rhythm returned The phonocardiogram (Fig 6) confirmed the auscultation The ECG (Fig 7) and VCG (Fig 8) suggested right ventricular hypertrophy The chest x ray film revealed cardiomegaly with marked prominence of the pulmonary artery and increased vascularity of the lungs The urinalysis blood count and blood chemistry were normal

Catheterization of the right side of the heart was performed on Aug 29 1962 This demonstrated a rise in oxygen saturation at the ventricular level and right ventricular systolic hypertension slightly below systemic level The pressures in the main right and left pulmonary arteries were both 26/6 mm Hg These findings were interpreted as compatible with a ventricular septal defect with a large left to-right shunt and pulmonary stenosis

A select angiocardiogram with injection into the right ventricle demonstrated a very much dilated right ventricle and main pulmonary artery branches Two sites of constriction in the region of the main pulmonary trunk were seen these were interpreted as being at the pulmonary annulus and at the supravalvular pulmonary artery The levocardiogram showed dense reopacification of the whole right ventricular chamber and pulmonary artery consistent with a left to-right shunt at the ventricular level

There was a transient improvement with a decrease in the cyanosis and a gain in weight even after digitalis was discontinued However over the next few weeks he was twice readmitted with signs of cardiac failure and probable bronchopneumonia and on each occasion he improved with oxygen antibiotics digitalis and Mercuhydrin The physical findings remained the same over the entire period of observation On his final admission at the age of 3 months he was in a moribund state with signs of bronchopneumonia and he died a few hours later

AUTOPSY CARDIAC FINDINGS The heart was triangular in shape The apex was pointing toward the left and was formed only by the right ventricle From the base of the heart the aorta and pulmonary trunk originated in normal relationship The superior and inferior venae cavae and the coronary sinus entered the right atrium The foramen ovale was barely probe patent the right atrium was moderately dilated The right ventricular wall averaged 3.5 mm in thickness The infundibulum was widened its transverse diameter measured about 1 cm internally the widening was fusiform and terminated in a pulmonary orifice that was 2.0 cm in circumference No pulmonary cusps were present (Fig 1 C) in their site was a grayish wall with a knobby ridge forming its distal edge and two shorter similar ridges coursing transversely proximal to this level The pulmonary trunk was wide measuring 2 cm in circumference the right and left pulmonary arteries were also of large caliber measuring 1.3 cm in diameter The pulmonary veins entered

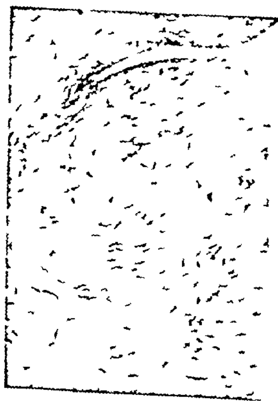


Fig 3 Pulmonary valve region (magnification X280) Note embryonic type of ...

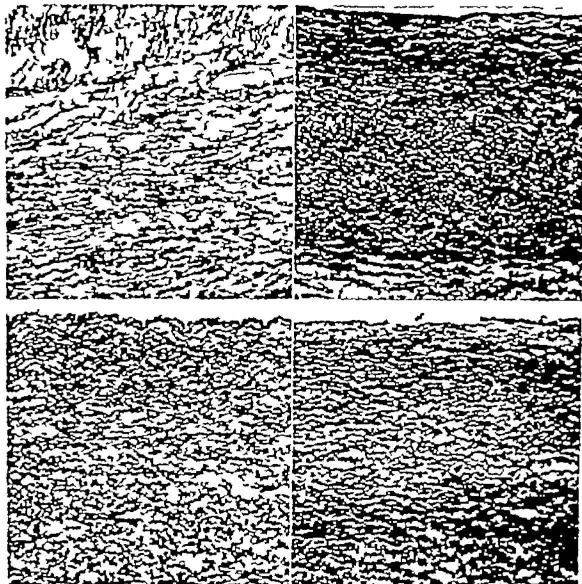


Fig. 4. Pulmonary trunk (magnification × 780). *Upper left*, Case 1. Transitional pattern, type A. *Upper right*, Case 2. Inner half of wall (above), aortic type. Outer half of wall, transitional pattern, type A. *Lower left*, Case 3. Transitional pattern, type A. *Lower right*, Case 4. Transitional pattern, type B.

the left atrium. The left ventricular wall averaged 3.5 mm. in thickness. In the subaortic region there was an interventricular septal defect (Fig. 2) which measured 1 cm. and which presented on the right side just inferior to the crista supraventricularis. The defect was located just proximal to the right posterior aortic commissure. The aortic valve measured 2.9 cm. in circumference. The coronary arteries took normal origin, and the arch was left-sided, giving rise to the brachiocephalic vessels in the normal sequence. The ductus arteriosus was obliterated. *The autopsy diagnoses was* (1) absence of pulmonary valve cusps, (2) tetralogy of Fallot, (3) marked dilatation of the pulmonary trunk, and (4) probe-patent foramen ovale.

Case 4. J. H. This 6-month-old male child was admitted on Jan. 15, 1963, with a history of almost continuous respiratory distress and intermittent fever over the preceding 2 months. He had had three previous hospitalizations, one for bronchopneumonia and two for bronchitis. The weight at birth was 6 pounds and 5 ounces, and on admission it was 1 pounds and 11 ounces.

On examination he was observed to be in moderate respiratory distress, with a respiratory stridor that was audible at a distance. Slight cyanosis was present. The heart rate was 150 per minute. The apical impulse was *in the sixth left intercostal space* just outside the mid-clavicular line. A systolic as well as a diastolic thrill were palpable in the left lower parasternal region. The second heart sound was single and very faint in the pulmonary area.

A long Grade 4/6 systolic murmur and Grade 3/6 early diastolic murmur separated by a definite silent gap were both heard best at the third left intercostal space. There were persistent rhonchi over both lungs. Slight hepatomegaly was present.

The ECG (Fig. 7) and VCG (Fig. 8) revealed right ventricular hypertrophy. X-ray examination of the chest showed obstructive emphysema of the right lower lobe with shift of the mediastinum to the left. The heart was moderately enlarged with a very prominent pulmonary artery segment.

Catheterization of the right side of the heart revealed right ventricular hypertension (84/3 mm. Hg). The pulmonary artery could not be entered. A pulmonary vein was entered via the foramen ovale and left atrium, and the pulmonary vein wedge pressure was 30/12 mm. Hg. There was a considerable oxygen step-up at the ventricular level, which suggested a large left-to-right shunt. Slight undersaturation (89 per cent) of the peripheral arterial blood was probably due to a small right-to-left shunt.

A selective angiocardiogram, with injection into the right atrium, demonstrated well-marked reopacification of the right ventricular outflow tract and pulmonary artery consistent with a large ventricular septal defect. The pulmonary trunk and its branches, especially the right, were extremely dilated, in marked contrast to the peripheral pulmonary arteries, which were relatively of much smaller caliber (Fig. 9).

He was treated with antibiotics, digitalis, and diuretics for several weeks with no change in the respiratory distress and pulmonary signs.

Bronchoscopy was attempted on Feb. 20, 1963, but was not completed because the trachea just above the bifurcation was seen to be very much narrowed, presumably by the huge pulmonary artery. After this procedure his condition deteriorated rapidly, and he was placed on the Bird respirator. He died the next day.

AUTOPSY CARDIAC FINDINGS. The heart was enlarged; it weighed approximately 50 grams. The apex was pointing toward the left. It was formed exclusively by the large right ventricle. The ascending aorta had an average diameter of 1.6 cm., the pulmonary trunk, 2.0 cm. When the heart was opened, the superior and inferior venae cavae and the coronary sinus were seen to enter into a dilated right atrium. The foramen ovale showed only a minute probe patency; a thick valve closed the fossa ovalis. The right ventricle was bulky; it averaged 3.5 mm. in thickness. The trabeculation was prominent. The infundibular portion was distended to a



Fig. 5. Posteroanterior films of the chest. *A*, Case 1. *B*, Case 2. *C*, Case 3. *D*, Case 5. Note the prominent pulmonary artery segment in Cases 1, 2, and 3 and mediastinal shift due to obstructive emphysema of the right lung in Case 2.



Fig 6 Case 3 Phonocardiogram showing the typical to-and-fro murmur

circumference of 4 cm chiefly but not exclusively above the level of the crista supraventricularis and the endocardium was thickened and white The crista supraventricularis was intact and flat surfaced From the infundibulum arose the pulmonary trunk 2.8 cm in circumference at its origin There were semilunar cusps or muses (Fig 1 D) The wall of the pulmonary artery which was thinner in this zone than more distally showed only some intimal irregularities and nodularity of its lining for a length of 1.3 cm maximum nodularity was at the distal end of this zone anteriorly and to the left The circumference of the pulmonary trunk at the distal end of this zone also measured 2.8 cm but the trunk promptly widened to a circumference of 4 cm between this level and the bifurcation The right and left main pulmonary arteries were also greatly dilated each easily admitting a probing finger The intrapulmonary arteries however appeared to be of normal caliber The ductus arteriosus was obliterated All pulmonary veins entered the left atrium The wall of the left ventricle averaged 5.5 mm in thickness There was a high interventricular septal defect it measured 1.2 by 0.8 cm and emerged on the right side below the crista supraventricularis The aortic orifice measured 2.5 cm in circumference the three semilunar cusps were well formed The coronary arteries originated normally The aortic arch was left sided *The autopsy diagnosis was* (1) absence of pulmonary valve cusps (2) ventricular septal defect (3) marked dilatation of the pulmonary trunk and (4) minute probe patent foramen ovale

Case 5 N F This female infant studied by Dr Lendrum at Michael Reese Hospital had been observed to be intensely cyanotic at birth On examination she was in mild respiratory distress and moderately cyanotic The peripheral pulses were normal the liver was not enlarged Palpation revealed gross cardiomegaly and a systolic thrill at the pulmonary area A Grade 3/6 to 4/6 systolic as well as a diastolic murmur with a to-and-fro rhythm were heard best at the third left intercostal space X-ray films of the chest showed considerable cardiomegaly with probable left ventricular enlargement The pulmonary artery segment was concave the superior vena cava appeared to be prominent and the lung fields were hypervascular The electrocardiogram indicated marked right ventricular and probable left ventricular enlargement A venous angiocardiogram obtained when she was 12 days of age revealed a large right atrium and a functionally if not anatomically single ventricle The aorta arose anteriorly and was continued as a right aortic arch The pulmonary trunk located posteriorly was dilated (Fig 10) The patient steadily deteriorated despite all therapy and died at 24 days of age

AUTOPSY CARDIAC FINDINGS The right atrium was greatly dilated and received all the pulmonary veins normally The atrial septum was almost absent being represented only by a rim of tissue superiorly A common atrioventricular valve consisting of 5 cusps was continuous across the two ventricles The ventricular component of the septal defect was huge the ventricular septum consisted only of a 1-cm high muscular ridge near the apex The aorta took origin anterior to the pulmonary trunk and both vessels came off the right ventricle The aortic valve had three cusps and the valve ring was 3 cm in circumference There was no right coronary ostium and the left one appeared to be enlarged There was an abnormal communication between the posterior aortic sinus of Valsalva and the right ventricle just below the origin of the pulmonary trunk The maximum thickness of the right and left ventricular walls were 1 and 1.1 cm respectively There were no pulmonary valve cusps these were replaced by a ridge of translucent tissue The pulmonary trunk at its origin was 2.8 cm in circumference but more distally was dilated to a circumference of 4 cm The ductus arteriosus was closed The aortic arch and descending aorta were right sided *The autopsy diagnosis was* (1) double-outlet right ventricle (2) common atrioventricular canal (3) absence of the pulmonary valve cusps (4) right aortic arch (5) single (left) coronary artery (6) abnormal aortic sinus of Valsalva–right ventricular communication (7) secundum type of atrial septal defect and (8) hypertrophy and dilatation of the right atrium and right ventricle with hypoplastic left atrium

Microscopic descriptions

Pulmonary trunk (Fig 4)

CASE 1 There was marked fragmentation and disorientation of the elastic membranes which were loosely arranged and frequently widely separated from one another by areas devoid of any elastic tissue and replacement chiefly by hypocellular connective tissue with relatively few muscle fibers *Evaluation* Transitional pattern type A according to the classification of Saldana and Arias-Stella[11]

CASE 2 The inner half of the wall showed uniformly parallel and intact elastic membranes whereas the outer half showed elastic membranes which appeared to be broken up *Evaluation* The inner half of the media is interpreted as aortic type whereas

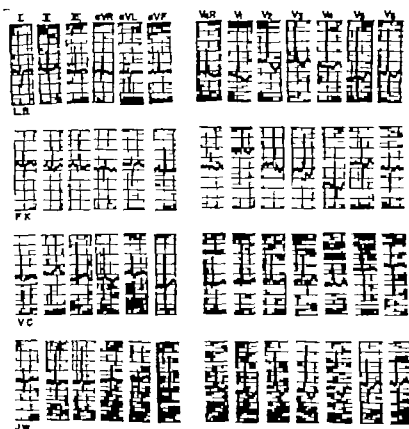


Fig 7 Electrocardiograms of Cases 1 2 3 and 4

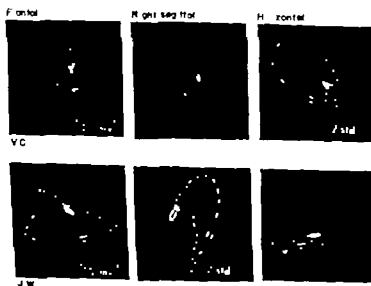


Fig 8 Vectorcardiograms of Cases 3 (V C) and 4 (J W)

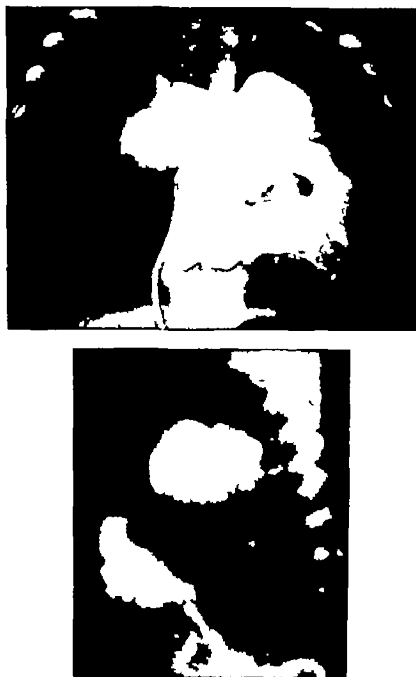


Fig. 9. Case 4. Selective angiocardiogram. *Top*, Posteroanterior view. Note huge pulmonary trunk, right pulmonary artery, obstructive emphysema of right lung with mediastinal shift to left. *Bottom*, Lateral view.

the outer half is a transitional A type of configuration. (This finding, especially in view of the extreme saccular dilatation of the pulmonary arteries which would tend to loosen the arrangement of the elastic fibers, was considered to be distinctly abnormal.)

CASE 3. The innermost elastic membranes (comprising the inner one sixth of the wall) were well preserved, being coarse, intact, and parallel to one another. The more external membranes, however, especially those in the outer half of the wall, were

extensively fragmented and scattered in apparently disoriented pattern. *Evaluation:* Transitional pattern, type A.

CASE 4. The elastic tissue content of the media was moderately dense. There was a frequent segmental narrowing of the individual elastic membranes, especially in the mid portion of the wall, with only occasional fragmentation. *Evaluation:* Transitional pattern, type B.

Intrapulmonary arteries. The microscopic appearance of the intrapulmonary arteries was similar in all four cases. The medium sized arteries, the lumens of which were markedly dilated, showed marked prominence of the elastic tissue with transition into the smaller arteries which showed a definite muscular pattern and increase in adventitial tissue.

Pulmonary valve region. Microscopically each of the pulmonary valve zones consisted of myxoid tissue of embryonic type (Fig. 3).

Cases 3 and 4 showed surprisingly uric acid infarcts in the kidneys. Such uric acid deposits, which do not actually represent true infarcts, are rare except in the neonatal period. Each of these two cases had accompanying bronchopneumonia. Possibly nuclear breakdown in the inflammatory cellular infiltrate in the lung was responsible for the urate deposit in the kidneys.

Discussion

Although a relatively small number of cases has been reported, the characteristic pathologic and clinical picture manifested by the absence of the pulmonary valve cusps should make it an easily recognizable entity, distinguishable from other causes of cardiac failure in infancy and childhood.

Of all the reported cases with absence of or rudimentary pulmonary valves, only 3 had no other associated anomaly. The most frequent coexisting lesion was a ventricular septal defect, which was present in all but 6 cases reported hitherto. Stenosis of the right ventricular outflow tract at the infundibulum was very frequently present; in most of these cases there appeared to be some overriding of the aorta. Such cases are presumed to be primarily instances of tetralogy of Fallot.

Other anomalies that have been described in association with absence of the pulmonary valves are patent ductus arteriosus, aneurysm of an aortic sinus of Valsalva, single coronary artery, common atrioventricular canal, tricuspid atresia, mitral atresia, and double-outlet right ventricle.

The prevalence of this condition in males is perhaps worthy of note. Of 36 reported cases of absence of the pulmonary valves in which the sex was stated (including our cases), 24 were males and 12 were females.

In 3 out of the 4 cases in this series studied histologically, the elastic tissue pattern of the main pulmonary trunk was of the transitional type. This is the type expected in this age group (3-6 months). However, in view of the marked degree of dilatation of the pulmonary trunk, it would appear that the absolute quantity of elastic tissue was probably increased, and this pattern may therefore be interpreted as abnormal in these cases.

The fourth case, showing the densest elastic tissue arrangement with aortic pattern in the inner portion of the wall, was the most striking and would strongly suggest the presence of pulmonary hypertension.

Catheterization of the right side of the heart in 3 of our cases revealed right ven



Fig. *10.* Case 5. Venous angiocardiogram. Note dilated pulmonary trunk immediately posterior and ascending aorta immediately anterior to the opacified superior vena cava.

tricular pressures at systemic levels and large left to right ventricular shunts (Table 1) The pulmonary trunk was entered only in Case 3 and the pressure was found to be normal establishing the existence of right ventricular outflow obstruction No attempt has been made by us or by others to quantitate the regurgitant flow

It has been generally accepted that if there are no pulmonary valves the right ventricular and pulmonary arterial pressures become equal at end-diastole Although this criterion is met in many instances several cases of absence of the pulmonary valves and ventricular septal defect have been found to have higher pulmonary arterial than right ventricular pressure at end-diastole If significant pulmonary stenosis exists the obstruction to retrograde flow could explain this In our Case 3 there was an end diastole gradient of 5 mm Hg The heart rate at that time was 150 per minute and it is possible that the end diastolic pressure would have equalized at a slower rate as Campeau[4] has suggested

The physical signs in our cases were similar to those described in previous reports[11,14] The second heart sound was single and often inaudible at the pulmonary area A loud rough to and fro murmur often accompanied by a thrill was best heard at the left sternal edge at the level of the second and third intercostal spaces

X-ray examination of the chest shows cardiomegaly with marked dilatation of the pulmonary trunk and its primary branches (Fig 5) The electrocardiogram provides evidence of right ventricular hypertrophy with rsR or less commonly qR patterns in right precordial leads (Fig 7) The infants are usually dyspneic and may have pulmonary râles hepatomegaly and even peripheral edema because of left and right heart failure Respiratory distress in many instances however is due mainly to an additional pulmonary factor Two of Miller's patients ages 2 months and 3 years respectively had obstructive emphysema of the left lung due to compression of the left bronchus by the huge pulmonary trunk One of our patients (J W Case 4) had obstructive emphysema of the right lung and severe stridor both presumably caused by the enormous right pulmonary artery It is probable that the transient collapse of the right lower lobe in Patient L B (Case 1) and the terminal episode involving the right lung in Patient F K (Case 2) were also pressure effects caused by the dilated right pulmonary artery *Compression of the tracheal bifurcation or* one of the main bronchi by the aneurysmally dilated pulmonary trunk and its main branches deserves emphasis because of its important bearing on prognosis An infant with tetralogy of Fallot no pulmonary valves and grossly enlarged main pulmonary arteries has a very poor prognosis if obstructive respiratory symptoms are present Older patients also have considerable enlargement of the pulmonary artery yet an onset in late childhood of obstructive respiratory manifestations has not been

Table I Catheterization findings in 3 cases

Patient and date of catheterization	Age	Pressures (mm Hg) RA Mean	RV	PA	FA	Oxygen saturation (%) SVC	RA	RV	PA	FA	Comments
V C Nov 29 1962	18 days	?5	84/3	27/8	98/56	—	55 6	68 9	71 3	93 1	LBF 1 7 / SBF
J W Feb 7 1963	6 mo	6 0	90/5	—	116/55	54 3	58 0	81 9	—	90 6	
L B Aug 9 1954	12 mo	0	7/7	—	—	79 3	79 1	79 3	—	—	Clinically very cyanotic

[illegible]
SVC Superior vena cava RA Right atrium RV Right ventricle PA Pulmonary artery FA Femoral artery

reported. This may be related to a greater rigidity of the tracheobronchial wall in older children and its resistance to deformation.

Smith and associates[7] described the case of an infant with absence of the pulmonary valve cusps, with no other associated lesion, who presented as an instance of intrauterine cardiac failure and died 30 minutes after birth. At birth and immediately after, the pulmonary hypertension which is physiologic at this stage would tend to aggravate the pulmonary regurgitation. Smith and associates suggested, moreover, that the free communication of the systemic and pulmonary arterial systems through the ductus arteriosus during fetal life would allow aortic blood to run off into the right ventricle via the pulmonary trunk. During the hours and days after birth the pulmonary vascular resistance and therefore the pulmonary arterial pressure may undergo a physiologic reduction and also the ductus arteriosus usually closes. Both factors would tend to ameliorate the pulmonary regurgitation and produce a clinical improvement. Such an improvement was observed over the first few weeks of life in Patient N. C. (Case 3), the only one of our patients who had been under continuous clinical observation since birth.

Three of Miller's patients (ages 6, 6, and 9 years) who had no pulmonary valves underwent open-heart surgical repair of their associated ventricular septal defects. The abolition of the left-to-right shunt and resection of the right ventricular obstruction led to a clinical improvement in these 3 patients. However, open-heart surgery in early infancy still carries a very high risk at the present time, and for very sick infants with absence of the pulmonary valves and left-to-right shunts, Venables[14] has suggested banding of the pulmonary artery as a palliative procedure. He suggests that this operation would not only reduce the left-to-right shunt, but also limit the regurgitant flow. These factors might alleviate heart failure but would not reduce the aneurysmal dilation of the pulmonary artery. Unless the compression of the bronchial tree is alleviated, an increased survival rate of the infants in distress is unlikely.

Summary

Clinical manifestations, diagnostic studies, and pathologic findings in 5 autopsy-proved cases of congenital absence of the pulmonary valves are summarized. Anatomically, only scattered flat nubbins or ridges, apparently representing rudimentary valve tissue, were found in a well-delineated annular zone in place of the normal semilunar pulmonary cusps. In each case, a large ventricular septal defect and aneurysmal dilatation of the main pulmonary arteries were present. Three and possibly 4 of the infants had tetralogy of Fallot as well and thus belonged to the increasingly recognized group of patients with this combination of lesions. The fifth infant had a severe form of common atrioventricular canal, double outlet right ventricle, and an abnormal aortic sinus of Valsalva–right ventricular communication in addition to absence of the valves.

Each of the patients died in early infancy (1 month to 6 months) and the cause of death was attributed to two factors: obstruction of the respiratory tract due to the aneurysmal pulmonary arteries and heart failure. Hence, the prognosis for infants with these findings appears to be poor. Characteristic auscultatory findings consist of a loud, rough systolic murmur and an early diastolic (to and fro) murmur which, together with absence of the pulmonary closure sound and normal systemic pulse pressure, strongly suggest an absence of the pulmonary valves. Markedly dilated pulmonary arteries are seen radiologically.

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Poststenotic dilatation of the aorta with muscular subaortic stenosis

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Functional obstruction to left ventricular outflow was described by Brock in 1957.[1] The lesion, characterized by a left ventriculo-aortic gradient in the absence of fixed anatomic obstruction, has subsequently been reported under a variety of names. It is most important to distinguish muscular subaortic stenosis from the fixed orifice types since surgical[2] and medical[3] management may differ in the two groups. Absence of poststenotic dilatation of the aorta has been emphasized as a necessary diagnostic feature of muscular subaortic stenosis. No case with dilatation of the ascending aorta has thus far been reported. On the contrary, the vessel is generally considered to be normal or small.[4] In addition, aortic ejection sounds, with a single exception, have been uniformly absent. The purpose of this report is to describe the unique occurrence of conspicuous dilatation of the ascending aorta in 3 documented cases of muscular subaortic stenosis, in one of which there was an associated aortic ejection sound.

Case reports

Case 1. A 43 year-old white woman was admitted to the Georgetown University Medical Center for cardiac evaluation in February 1963. Angina and effort dyspnea had begun 2 years previously and progressed to orthopnea and paroxysmal nocturnal dyspnea. Digitalis and sodium restriction resulted in symptomatic improvement until October 196?, when the symptoms returned. Three weeks prior to her hospitalization, she experienced two syncopal episodes. Her medical history was otherwise negative and there was no prior history of rheumatic fever, hypertension, or heredofamilial cardiovascular disease. Review of systems was noncontributory.

PHYSICAL EXAMINATION. The blood pressure was 110/80 mm. Hg, the pulse rate was 64 per minute, and the rhythm was regular. The patient was normally developed and able to lie flat without respiratory distress. The chest was normal. The jugular venous pulse showed a dominant A wave, but the mean venous pressure was normal. The arterial pulse was brisk with a perceptible double impulse. Palpation of the precordium revealed a gentle systolic lift in the second right intercostal space over the aortic root. Three centimeters beyond the midclavicular line there was a moderate left ventricular lift with easily palpable presystolic ventricular distention. A systolic thrill was detected at the lower left sternal border and at the cardiac apex. Auscultation revealed a Grade 5/6 crescendo-decrescendo apical systolic murmur. Both a third heart sound

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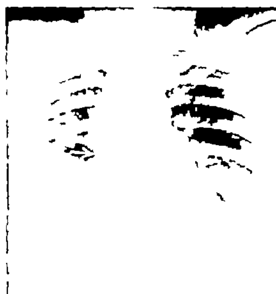


Fig 1A Case I Roentgenogram of the chest in posterior anterior projection showing cardiomegaly and dilatation of the ascending aorta (arrow)

nd an atrial sound were clearly heard The ejection tolic murmur was loudest at the lower left sternal border but was less than Grade 3 at the base with light radiation into the neck An aortic ejection sound was periodically sought but was neither heard nor recorded The second sound in the pulmonary area was paradoxically split and the aortic component had a tambour quality A diastolic murmur of aortic insufficiency was not audible

LABORATORY DATA The hematocrit was 38 per cent The white blood cell count was 9,700 with a normal differential Corrected sedimentation rate (Wintrobe) was 26 mm in 1 hour Urinalysis VDRL fasting blood sugar blood urea nitrogen and serum electrolytes were normal The electrocardiogram showed P-R interval 0.18 second There was left ventricular hypertrophy and strain Posteroanterior and oblique x-ray films of the chest showed left ventricular enlargement (Fig 1A) with no displacement of the barium filled esophagus Fluoroscopic examination revealed no valvular calcification There was obvious post stenotic dilatation of the aorta especially in the left anterior oblique view

The patient underwent transseptal left heart catheterization The contour of the brachial arterial pulse suggested muscular subaortic stenosis The onset to peak was short and the rate of rise was normal The postpremature beat brachial arterial tracings showed the consistent declines in pulse pressure diagnostic of muscular subaortic stenosis[16] The resting cardiac index was 3.0 L/min/M² The left ventriculo-aortic systolic gradient was 128 mm Hg and the right ventricular and pulmonary arterial systolic pressures were 48 and 15 mm Hg respectively indicating associated obstruction to right ventricular outflow Selective left ventricular angiocardiograms revealed conical narrowing of the outflow tract The valve cusps appeared to be normal The aortic root was dilated to over twice the size of the descending thoracic aorta (Fig 2A) The diagnostic conclusion was muscular subaortic stenosis dilatation of the ascending aorta and associated subvalvular pulmonary stenosis

In May 1963 the patient underwent cardiac surgery utilizing cardiopulmonary bypass Cardiac arrest was induced by cold The aorta was described as being dilated and slightly thin It was opened and the valve was found to be normal Approximately 1.5 cm below the aortic leaflets there was a 1 cm wide circumscribed area of thickened endocardium (Fig 3) This fibrous area was removed and the hypertrophied muscle beneath was excised in a linear fashion from well down in the ventricle to the insertion of the aortic cusps removing a strip approximately 7 mm wide After closure of the aortotomy incision the heart was rewarmed and a single defibrillating shock restored a normal sinus rhythm The postoperative course was uneventful

The patient returned to the hospital for re-evaluation in March 1964 She had experienced a marked decrease in the frequency of both angina and effort dyspnea Syncope had not occurred since the surgical procedure The only therapy had been oral diuretics twice weekly On physical examination the blood pressure was 120/60 mm Hg Palpation of the precordium placed the left ventricular lift at the mid-clavicular line as compared with findings of the previous examination which had localized it 2 cm beyond this point A faint decrescendo diastolic blowing murmur was now audible along the lower left sternal border The auscultatory findings were otherwise unchanged from those described preoperatively The electrocardiogram showed a P-R interval of 0.21 second and a QRS duration of 0.12 second The left bundle branch block which had appeared

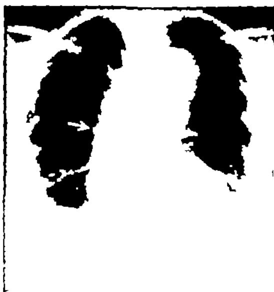


Fig 1B Case II Roentgenogram of the chest in the posterior anterior projection showing cardiomegaly and dilatation of the ascending aorta (arrow) and arch



Fig. 1C. Case III. Roentgenogram of the chest in posterior anterior projection showing cardiomegaly and dilatation of the ascending aorta (*arrow*).

postoperatively was still present. Posteroanterior and oblique x-ray films of the chest showed a slight decrease in heart size. The left ventricle was interpreted as being normal. Dilatation of the ascending aorta was still apparent.

The patient underwent transseptal left heart catheterization. The contour of the brachial arterial pulse was characteristic of muscular subaortic stenosis, and postpremature beats revealed the diagnostic declines in pulse pressure. The systolic gradient varied spontaneously from 0 to 80 mm. Hg. The cardiac index was 2.84 L./min./M.² at which time the orifice size was estimated to be 0.6 cm.² During the Valsalva maneuver[14] the gradient increased from 80 to 108 mm. Hg. During infusion of pressor amine the gradient decreased from 92 to 15 mm. Hg.

Case II. A 58-year-old white woman was admitted to Georgetown University Medical Center for cardiac evaluation in June, 1963. Her history had begun 1 year previously with episodes of exertional dyspnea and lightheadedness. Breathlessness was progressive with subsequent development of ankle edema, paroxysmal nocturnal dyspnea, and dull precordial effort pain which radiated into the left arm and lasted 5 to 15 minutes. Digitalis and diuretics resulted in symptomatic improvement. The patient had no prior knowledge of rheumatic fever, hypertension, or heredofamilial cardiovascular disease. Past medical history was negative except for gastrectomy (duodenal ulcer) and a cholecystectomy which were performed without complication in 1936.

PHYSICAL EXAMINATION. The blood pressure was 130/80 mm. Hg, the pulse rate was 80 per minute, and the rhythm was regular. The patient was moderately obese. The chest was normal. The jugular venous pulse showed a small dominant A wave, but the mean venous pressure was normal. The arterial pulse was not quick rising. The cardiac apex was at the mid-clavicular line with a moderately sustained left ventricular lift and palpable presystolic ventricular distention. There was no thrill. Auscultation at the cardiac apex revealed prominent atrial and third heart sounds. The second heart sound at the pulmonary area was paradoxically split. At the base was a relatively short Grade 3/6 crescendo-decrescendo systolic murmur which radiated slightly into the neck. The murmur was of equal intensity along the left sternal border. No ejection sound was detected, and the diastolic murmur of aortic insufficiency was absent. There was 1+ bilateral pretibial edema.

LABORATORY DATA. The hematocrit was 41 per cent, and the white blood cell count was 9,200 with a normal differential. Urinalysis showed 7 to 9 white blood cells per high power field but was otherwise normal, including subsequent cultures. A VDRL, fasting blood sugar, blood urea nitrogen, and serum electrolytes were normal. The electrocardiogram showed right bundle-branch block. The P-R interval was 0.17 second. Left ventricular hypertrophy was not present. Posteroanterior, lateral, and oblique x-ray films of the chest showed left ventricular enlargement and marked elongation, tortuosity, and dilatation of the aortic arch (Fig. 1B). Catheterization of the left side of the heart was done by the percutaneous retrograde femoral technique. The systolic gradient across the left ventricular outflow tract varied spontaneously from 0 to 30 to 50 mm. Hg. The gradient increased with the Valsalva maneuver[14,15] during the inhalation of amyl nitrite and with the infusion of Isuprel. Postextrasystolic beats revealed the reproducible declines in pulse pressure diagnostic of muscular subaortic stenosis.[15] The resting cardiac index was 2.35 L./min./M.²



Fig. 4. Case I. Left ventricular angiocardiogram demonstrating dilatation of ascending aorta. The left atrium was visualized as the catheter recoiled during injection.



Fig. 2B. Case II. Left ventricular angiocardiogram showing dilatation of ascending aorta, particularly in arch.

Selective left ventricular angiocardiography revealed conspicuous dilatation of the ascending aorta extending beyond the region of the left subclavian artery (Fig. 2B). The diagnostic conclusion was muscular subaortic stenosis with dilatation of the ascending aorta.

Case III. A 33-year-old white man was admitted to the Georgetown University Medical Center for cardiac evaluation in March, 1964. A cardiac murmur had been recognized when he was 28 years old, but he remained asymptomatic until 5 months prior to admission, when he was hospitalized at another institution because of a crushing substernal chest pain which lasted 45 minutes. The diagnosis of aortic stenosis was made and he was discharged after a week on medication other than phenobarbital. Subsequently, he experienced occasional episodes of effort dyspnea and substernal discomfort at rest but denied angina or syncope. His medical history was otherwise negative, and there was no recollection of rheumatic fever, hypertension, or bothered of cardiovascular disease. Review of systems was noncontributory.

PHYSICAL EXAMINATION. The blood pressure was 130/80 mm. Hg, the pulse rate was 80 per minute, and the rhythm was regular. The patient was normally developed and able to be flat without respiratory distress. The chest was normal. The jugular venous pulse showed a dominant A wave, but the mean venous pressure was normal. The arterial pulse was clearly quick-rising, but a double impulse could not be felt. Palpation of the precordium revealed a gentle systolic lift in the second right intercostal space over the aortic area. There was a slight left ventricular lift at the midclavicular line. Presystolic ventricular distention was not palpated. There were no thrills. An ejection systolic murmur was loudest at the lower left sternal border, where it was Grade 3 in intensity. The murmur was Grade 1 at the base and Grade 2 at the apex. There was no transmission into the neck. Neither a third heart sound nor an atrial sound was audible. An aortic ejection sound (Fig. 4) was easily heard at the apex and left sternal border but was not heard at the base. The second heart sound was single and had a tambour quality in the aortic area. A diastolic murmur of aortic insufficiency was not audible. On occasional subsequent examinations the aortic ejection sound was absent. At these times the systolic murmur was longer and an atrial sound was present.

LABORATORY DATA. The hematocrit was 45 per cent. The white blood count was 6,500 with a normal differential. Corrected sedimentation rate (Wintrobe) was 1 mm. in 1 hour. Urinalysis, VDRL, fasting blood sugar, blood urea nitrogen, and serum electrolytes were normal. The electrocardiogram showed a P-R interval of 0.20 second and was otherwise normal. Posteroanterior and oblique x-ray films of the chest showed minimal left ventricular enlargement (Fig. 1C) with no displacement of the barium-filled esophagus. Fluoroscopic examination revealed no valvular calcification. There was obvious poststenotic dilatation of the aorta, especially in the left anterior oblique view.

The patient was studied by transseptal left heart catheterization. Thoracic aortography was performed after percutaneous retrograde femoral arterial catheterization. The systolic gradient across the left ventricular outflow tract varied spontaneously from 0 to 50 mm. Hg. The cardiac index was 2.6 L./min./M². The gradient increased from 15 to 60 mm. Hg during the Valsalva maneuver[13,14] and increased from 15 to 150 mm. Hg after the sublingual administration of nitroglycerin.[14] Postpremature beats revealed the reproducible declines in systemic arterial pulse pressure diagnostic of muscular subaortic stenosis.[15] Thoracic aortography visualized dilatation of the ascending aorta (Fig. 2C).

Discussion

In 1957 Brock called attention to obstruction of left ventricular outflow due to muscular subvalvular hypertrophy. Since



Fig. 2C. Case III. Thoracic aortogram showing dilatation of the ascending aorta.

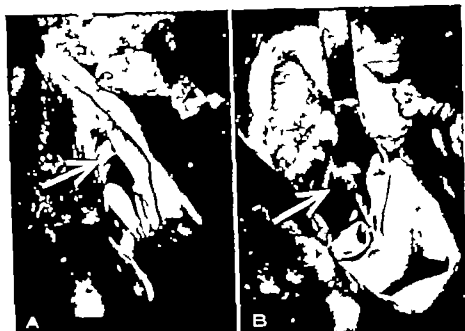


Fig 3 Case I 1 Normal aortic leaflet retracted Fibrous thickening of endocardium visible in the upper left quadrant below the valves (arrow) B Strip of myocardium and fibrous segment resected Incision in myocardium seen at 10 o clock (arrow)

that time over 100 cases have been reported and many others have surely been recognized in clinical practice Poststenotic dilatation and aortic ejection sounds have thus far been conspicuously lacking Indeed their absence has been considered to be important diagnostic information [4,5] During the past 3 years we have studied 11 patients with proved muscular subaortic stenosis 3 of whom have had associated dilatation of the ascending aorta One of these 3 had an aortic ejection sound In valvular aortic stenosis poststenotic dilatation is an accepted feature [11] Its incidence has been estimated to be as high as 84 to 92 per cent in the acquired group [11, 8] and 74 per cent in the congenital group [11] Since dilatation of the ascending aorta occurs in both congenital fixed orifice subvalvular stenosis [1] and congenital valvular stenosis its presence cannot be used to distinguish one from the other [11,12] Poststenotic dilatation rarely occurs in supravalvular aortic stenosis and until the observations herein reported had not been observed in muscular subaortic stenosis In 2 patients (Cases I and III) the

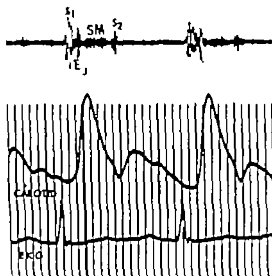


Fig 4 Phonocardiogram taken at lower left sternal border with indirect carotid pulse and electrocardiogram (Lead II) as reference tracings Note the systolic ejection sound (0 06 second after the onset of the first heart sound) which was recorded only in this area and at the apex The crescendo-decrescendo ejection murmur which peaks in mid systole was of greatest amplitude in this area

dilatation involved the ascending aorta up to the brachiocephalic vessels (Figs. 2A and 2C). In Case II (Fig. 2B) the dilatation continued beyond the left subclavian artery before gradually decreasing to the caliber of the distal thoracic aorta, which was of approximately normal size. One of the 3 patients (Case III) had an aortic ejection sound (Fig. 4). An ejection sound in muscular subaortic stenosis has been reported only once in the previous literature, and it is noteworthy that the ascending aorta was described as being normal. In this reported case, as in our own, the ejection sound was heard at the apex but not at the base. It was of additional interest in our patient that the ejection sound was not always audible. Its absence seemed to relate to periods of increased obstruction of outflow, since the disappearance of the ejection sound coincided with an increase in the intensity and duration of the systolic murmur and with the appearance of a prominent atrial sound. In Case I, the area of endocardial thickening found in the outflow tract was believed to be of no hemodynamic importance. Although areas of fibrous thickening have been described in association with muscular subaortic stenosis,[1] the significance of this morphologic finding is not yet clear. The associated obstruction to right ventricular outflow was an additional feature of interest in Case I.

Summary

The 3 cases which constitute this report represent the first examples of dilatation of the ascending aorta associated with muscular subaortic stenosis. Heretofore the absence of poststenotic dilatation has been considered to be a necessary feature of this type of left ventricular outflow obstruction. In one of the cases there was an associated aortic ejection sound, the presence of which has generally been considered to be strong evidence against the diagnosis of muscular subaortic stenosis. Although the absence of aortic ejection sounds and the absence of poststenotic dilatation of the aorta remain useful clinical signs, the observations herein described indicate that their presence no longer excludes muscular subaortic stenosis as a diagnostic possibility.

It is a pleasure to acknowledge the assistance of Dr. Modestino G. Criscitiello, Dr. Antonio C. de Leon, and Dr. James A. Ronan during the diagnostic procedures and to thank Mr. Bernard Salb for the preparation of the photographic illustrations.

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The spread to appearance time ratio in the estimation of left-to-right shunts

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A number of ingenious methods for calculating the actual size of a left-to-right shunt from indicator-dilution curves has been reported.[1,2] These methods utilize parameters of the curve itself that are believed to be influenced by the dynamics of the shunt flow. However, because of the variation in the mixing characteristics of large and small shunts and the resulting distortion of the contours of the shunt dye curve, a confusing variety of formulae has been advanced for the calculation of these shunts.

The contour of the dye curve itself has been shown experimentally to be altered by mixing alone, independent of cardiac output or the physical volume between injection and sampling sites (central volume).[4] In 1958 Shillingford[1] found that another variable, the appearance time of the curve, was also influenced by mixing. On the basis of model studies the simple ratio of the spread or width of the curve to its appearance time (referred to as Spread/AT) was proposed empirically as a semiquantitative estimate of the degree of mixing produced by mitral regurgitation in patients if the injection was made into the pulmonary artery and recording was done at the ear. Subsequent studies in models have shown that this inverse effect on spread and appearance time depends primarily upon the actual turbulence generated by the regurgitant jet itself in the atrium.[6] These studies demonstrated further that any primary source of mixing in the circulation, such as a left-to-right shunt, for example, will produce the same alterations in the peripheral dye curve.

It seemed reasonable to apply this ratio empirically to the study of left-to-right shunts in patients with congenital heart disease. The purpose of this paper is to show that the ratio may, in fact, be used as the most simple, accurate, indirect estimate of such a shunt by demonstrating a favorable comparison between the Spread/AT ratio and the per cent shunt calculated by the Fick method.

Material and methods

Thirty-four patients with left-to-right shunts due to congenital heart disease were studied by catheterization of the right

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[illegible]

side of the heart. No patients with known complicating right-to-left shunts or valvular regurgitation were included. The subjects ranged in age from 15 months to 47 years. Four patients had catheter diagnoses of patent ductus arteriosus, 12 had ventricular septal defects, and 18 had atrial defects. Measurements of pressure and blood oxygen saturation were made before recording dye-dilution curves. Oxygen saturation was determined by a Waters Conley oximeter and confirmed by the Van Slyke method. Gas analysis was obtained by the Scholander microtechnique. Cardiac outputs were determined by the Fick method, and left-to-right shunts were expressed as the per cent of total or pulmonary flow. Only shunts greater than 20 per cent were included because of the difficulty in assessing the smaller shunts by oxygen saturation methods.[7]

Peripheral dye curves were monitored by a Cambridge photoelectric earpiece with the Mark II amplifier and recorder.[* 8] Serial slug injections of 2 per cent Coomassie blue dye were made by flushing the dye with saline through a Rodriquez (multiperforate) catheter into the right or left main pulmonary artery (PA) and into the right ventricular (RV) and right atrial (RA) inflow tracts in sequence on withdrawal of the catheter. Considerable care was taken to try to place the tip of the catheter in the same positions for each patient. The techniques of injection and calibration of the earpiece dye curve by the end tail method have been described.[9] An electronic timer recorded precisely the arrival of the bolus of dye in the cardiac chamber. The injection technique is simple enough to permit an injection time of approximately 0.1 second per cubic centimeter of dye or a total injection time of less than 0.5 second (the average injectate was 2.0 c.c.).[11]

In all patients who had left-to-right shunts the earpiece curves recorded from central injections were found to have disappearance slopes interrupted by a "shoulder" or a "break" in one or more of the curves recorded from the three injection sites. This shoulder has been seen in this laboratory only in patients with intracardiac shunts and never in normal patients or in patients with valvular regurgitation.[1] The final disappearance slope line defining the "total curve" could be drawn easily before the onset of systemic recirculation, and the spread of each curve in seconds was measured on the semilogarithmic replot at 1/10 of the curve's peak. The Spread/AT ratio of Shillingford, defined as the spread divided by the appearance time, was calculated for all curves from injections into the pulmonary artery, the right ventricle, and the right atrium.[4]

In addition, one of the previously reported methods of estimation of shunts was chosen for comparison, and the build-up time (BT), peak concentration (C_p), and concentration on the disappearance slope equal to twice the build-up time ($C_p + C_{2BT}$) were measured on all curves as defined by Carter and his associates.[3] Through use of the formula ([illegible] $_{2BT}$) divided by ([illegible] the disappearance ratio was calculated. The spread, the appearance time, and the Spread/AT and disappearance ratios were plotted against the Fick per cent left-to-right shunt for each patient, and correlation coefficients were calculated.

Results and interpretations

Fig. 1 shows the peripheral dye curve from the injection of Coomassie blue dye into the left pulmonary artery of a 5-year-old girl (I. G., Table I) with a 50 per cent left-to-right shunt through a patent ductus arteriosus. The curve shows a shoulder high on the disappearance slope or a "double peak," and is typical of one variety of left-to-right shunt curve recorded by the Cambridge earpiece in this laboratory. This pattern has been seen with atrial and ventricular septal defects as well. The peak deflection of this curve is reduced below the maximal concentration expected, reflecting the increased volume of blood flow through the pulmonary circulation resulting from the left-to-right shunt.[12] The second peak or shoulder is produced by the shunt flow itself, since some of the dye reaching the aorta has been shunted through the ductus and back through the pulmonary circulation. In effect this is a reinjection of a smaller amount of dye into the pulmonary artery. The time between the two peaks [illegible]ates the circulation time of the shunt

*Cambridge Instrument Company.

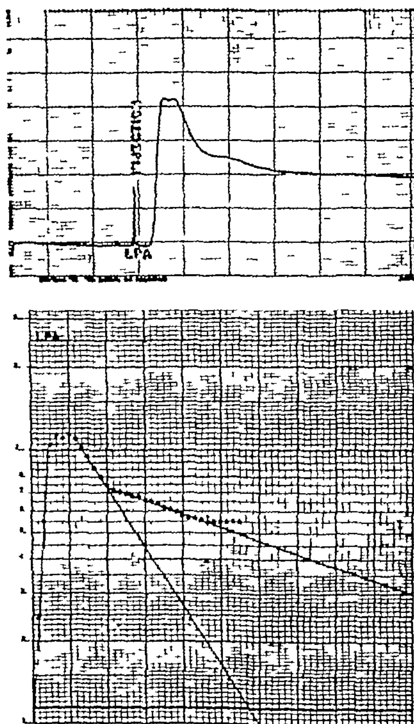


Fig. 1. Direct recording and semilogarithmic replot of the [illegible] dye curve from injection into the left pulmonary artery of patient (J.G.) with a 30 per cent left-to-right shunt through a patent ductus arteriosus. The second peak or shoulder is produced by the shunt flow passing through the ductus and the time between the peaks indicates the 2 second circulation time of the shunt. Chart lines are at 1 second intervals. A linear disappearance slope can be drawn on semilogarithmic replot before the onset of the secondary peak or systemic recirculation at 13 seconds.

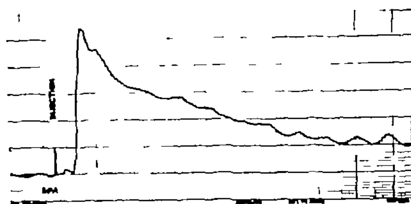


Fig. 2 The earpiece curve and semilogarithmic replot from injection into the left pulmonary artery of a patient (V. P.) with a 54 per cent left-to-right shunt through an atrial septal defect showing the typical shoulder high on the disappearance slope. There is clear delineation of the disappearance slope before the onset of systemic recirculation 14 seconds later

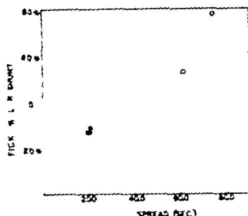


Fig. 3. The spread measured at 1/10 of the peak for the total curve from injection into the pulmonary artery plotted against the Fick per cent left-to-right shunt for the patients in Table I (r = + .51).

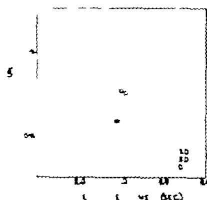


Fig. 4. The appearance time from injection into the pulmonary artery plotted against the Fick per cent left-to-right shunt (Table I; r = − .34).

The disappearance slope from the second peak defines a straight line on the semilogarithmic replot which can be drawn easily before a secondary break occurs 13.0 seconds after the beginning of the upstroke. The secondary break times well with the familiar recirculation hump seen in curves from *normal* patients with similar systemic cardiac indices and appearance times.* The secondary break, therefore, is believed to represent systemic recirculation in the shunt curves also. The disappearance slope line of the total curve could be considered to reflect the exponential washout of the system occurring before systemic recirculation. The spread of the curve defined by this slope line is 34.3 seconds. The appearance time for the curve is 3.8 seconds. The Spread/AT ratio is 34.3 divided by 3.8, or 9.0.

Fig. 2 shows the earpiece curve from injection into the left main pulmonary artery of a 41-year-old woman (V. P., Table I) with a 54 per cent left-to-right shunt through an atrial septal defect. This curve demonstrates a variation of Fig. 1 and shows the typical shoulder seen in earpiece shunt curves from central injection. It has also occurred in patients with ventricular septal defect and patent ductus. A disappearance slope line can be drawn clearly for the total curve before the onset of the secondary break. The appearance time is 5.2 seconds and the Spread/AT ratio for the total curve is 8.0. Similar calculations for the other patients with left-to-right shunts are entered in Table I. The patients are grouped according to the position of the defect. Using the entire curve prior to systemic recirculation, it will be seen that the calculated Spread/AT ratio varies to some extent depending upon the chamber of injection.

Fig. 3 shows a graph of the spread of each curve recorded after injection into the pulmonary artery taken at 1/10 of its peak on the semilogarithmic replot plotted against the Fick per cent shunt. Although

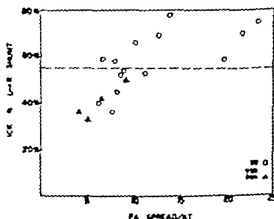


Fig. 5. Comparison of the Spread/AT ratio from injection into the pulmonary artery with the Fick per cent left-to-right shunt showing almost a linear correlation for shunts between 20 and 55 per cent (r = + .79). A ratio of 5.0 indicates a shunt of approximately 30 per cent, 7.5 a shunt of 43 per cent, and 10.0 a shunt of 60 per cent.

*Unpublished data.

Table I

Patient	Age (yr)	Diagnosis	Appearance time			Spread PA	Spread/appearance time			Cardiac index		PT / CP + 2BT / CP	Fick L-R shunt ( )
			PA	RV	RA		PA	RV	RA	Syst	Pulm		
I G	5	PDA	3 8	4 1	4 4	34 3	9 0	7 9	7 1	4 3	8 /	395	50
B G	10	PDA	3 4			21 4	6 3			5 9	10 2	373	42
D N	24	PDA	3 3	5 1	5 4	13 5	4 1	3 0	2 6	3 0	4 7	462	36
D T	5	PDA	3 6		4 7	18 0	5 0		4 6	4 5	6 8	571	33
J M	5	VSD	4 0	4 0	4 6	72 0	18 0	16 4	13 1	3 7	12 5	673	/0
C B	11	VSD	3 5	4 0		87 3	23 5	12 5		4 2	14 4	556	70
C C	9	VSD	4 0	4 7	4 8	46 8	11 7	13 8	11 3	3 1	7 6	830	58
K H	3	VSD		3 8	4 8			14 6	8 6	3 6	7 2		50
J A	39	VSD	5 0	6 0	6 0	38 0	7 6	6 8	8 8	4 6	8 0	584	47
C A	2	VSD		2 8	2 8			9 4	11 3	5 4	8 9		37
E E	38	VSD	5 0	6 5	6 0	26 0	5 2	3 1	6 0	4 2	6 5	487	36
R R	12	VSD	4 5	6 0	7 1	29 7	6 6	4 7	4 5	2 8	4 3	456	34
C C	15	VSD	4 5	5 8	5 0	20 3	4 5	3 4	5 0	4 3	6 1	457	29
J B	4	VSD	3 8	5 6	5 0	70 0	5 8	3 9	4 4	3 5	4 9	610	27
K B	9	VSD	5 0	5 7		15 5	3 1	3 7		3 2	4 2	259	25
M S	13	VSD	5 2			21 3	4 1			3 2	4 2	152	22
K Z	12	ASD	5 4	6 2	5 4	74 0	13 7	8 0	6 9	3 0	13 7	540	78
J M	5	ASD	2 8	4 4	4 5	65 0	23 2	11 2	9 5	3 2	12 6	59	75
M S	1	ASD	2 3	3 0	2 3	49 5	21 5	18 4	15 2	3 4	11 1	600	/0
F G	47	ASD	4 5		4 3	56 3	12 5		12 3	1 7	5 6	510	69
P P	8	ASD	3 5	3 6	3 8	35 0	10 0	6 5	7 8	3 6	10 7	548	66
J Z	15	ASD	2 3	4 3	4 7	49 0	19 6	8 1	7 2	2 8	6 9	478	59
R D	5	ASD	3 5	4 3	3 8	23 1	6 6	6 9	6 9	3 4	8 4	533	59
P M	20	ASD	4 3		6 5	38 /	9 0		5 6	3 8	8 9	695	58
G S	18	ASD	4 3	5 5	4 5	33 5	7 8	9 8	11 0	2 4	5 8	403	58
V P	41	ASD	5 2	5 8	6 0	41 6	8 0	7 0	6 7	3 9	8 6	655	54
R M	6	ASD	5 5	5 6	5 5	61 1	11 1	1	6 8	3 3	7 1	578	53
D M	10	ASD	3 7	3 7	4 3	31 8	8 6	6 5	6 1	1 8	2 9	360	57
E Y	76	ASD	5 8		6 8	47 0	8 1		8 4	2 8	5 2	513	45
P R	11	ASD	4 0	4 6	4 5	35 6	8 9	7 4	6 7	3 9	6 7	416	41
T S	6	ASD	4 2	4 5	4 5	25 6	6 1	4 9	5 3	3 5	5 8	44	40
A G	38	ASD	4 4	5 2	6 0	33 4	7 6	5 7	5 5	2 6	4 0	661	36
A M	7	ASD	6 6	8 5	7 6	50 2	7 6	5 1	5 1	3 2	4 6	405	32
L B	7	ASD	4 0	4 9	4 5	19 6	4 9	4 5	4 6	2 2	1 6	238	27

See text
PDA P[illegible] d ctus art[illegible] VSD V[illegible] tricular sept l d fect ASD Atrial septal d fect

there is some correlation (r = + 51) the scatter is too great to make this measurement a practical estimate of the size of the shunt In Fig 4 the appearance time from injection into the pulmonary artery is plotted against the Fick per cent shunt (r = − 34) Note that in general in the larger shunts the appearance time tends to be shorter but the correlation is not high enough to make this measurement useful in predicting the size of the shunt either

The correlation coefficient for the Fick to disappearance ratio C + m T C_p was found to be only + 46 Actually the presence of the well-defined shoulder in all centrally injected curves made calculation of the disappearance ratio a little more difficult whereas the spread at 1/10 of the curve s peak could be measured easily on any curve regardless of where the disappearance slope shoulder occurred

Fig 5 shows the calculated ratio of spread to appearance time of all curves from injection into the pulmonary artery plotted against the Fick per cent left to

of this calculation assumes that the left to right shunt itself is the primary source of mixing and diffusion present in the circulation.

Summary

An evaluation of the Spread:AT ratio from earpiece dye-dilution curves in patients with left to right shunts is presented and the simplest method of calculating the size of a shunt from one pulmonary artery curve regardless of cardiac output has been found. A significant correlation between this ratio and the Fick per cent left to right shunt has been demonstrated in 34 patients who had shunts over 70 per cent of total pulmonary flow. The inverse relationship between these two measurements, spread and appearance time, is believed to be caused by the mixing or turbulence created by the shunt itself, is discussed. The fact that a reasonable estimate of the size of the shunt regardless of cardiac output may be made quickly from one pulmonary artery earpiece curve emphasizes the practical significance of this simple method.

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A modern approach to the injection treatment of varicose veins and its applications in pregnant patients

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In reintroducing injection therapy as a treatment for varicose veins it is important to make quite clear that we are fully aware that injection therapy has been used before and has become widely and justifiably discredited. It is also important to point out that the old injection treatment gained popularity and support because of the early improvement enjoyed by patients after the initial thrombotic reaction in the vein had settled down. Follow up of these patients has resulted in the discovery of a high rate of recurrence after 6 months and in some the condition has been made a great deal worse than before treatment commenced. Nevertheless investigation of the occasional successful case might well have revealed the secret of its success, knowledge of which would probably have altered the incidence of recurrence. The reasons for the discredit of the old injection therapy will be made clear later in this communication.

It is essential to explain as briefly and clearly as possible the complex mechanism by which blood is returned from the lower limbs to the heart since this is a prerequisite to the understanding of the causes of varicose veins. The term *varicose veins* like chronic mastitis has been so widely used for so long that it is here to stay. It is an unfortunate terminology since it draws attention to one of the less important features of the disease. We are all aware that the patients with the greatest varicosities are not necessarily the most disabled and that frequently in the very worst cases there are no varicosities. It would be wiser to introduce the term *chronic venous insufficiency* (CVI) which indicates that the primary abnormality is a defect in the mechanism of venous return from the leg.

There are in each segment of the leg one or more synchronized pumping systems: in the foot the plantar pump, in the leg the peroneal, soleal, anterior and posterior tibial pumps, and in the thigh the quadriceps and adductor pumping system. In fact every myofascial compartment is in itself a pump. If the valves of the pumps become injured their reserve power is greatly reduced but in the initial state there is no loss of clinical function because the pumps like all other organs in the body

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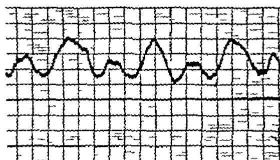


Fig 1 Normal pedal trace recorded in the long saphenous vein in the middle third of the leg The straight line represents zero pressure and each large square is equivalent to a pressure of 10 mm Hg

are designed with a capacity much greater than is necessary for ordinary function

The pumps register very low pressure in their diastolic phase During this phase blood is readily drawn in from the superficial veins As soon as muscle contraction takes place the valves in the perforating veins close and filling from the superficial system ceases The result of this is that during walking the pressure in the superficial veins drops to near zero twice with each step (Figs 1 and 2) During this period of low pressure the walls of the superficial veins recover their tone If low pressure is not rhythmically achieved during walking pathologic changes will take place in the veins

The essential abnormality in chronic venous insufficiency is the inability of the multiple pumping systems to reduce pressure in *the superficial veins to near zero* after the commencement of walking This happens most commonly as a result of damage to the valves in the perforating veins or to valves in the termination of the saphenous veins (Fig 3)

It is not widely appreciated that damage to the valves in the perforating veins is more important than damage to the valves at the termination of the long and short saphenous veins The reason for this in our opinion lies in the method of diagnostic study commonly employed Diagnosis of venous insufficiency is usually made upon the static limb and the rate of retrograde filling from the saphenous opening can be demonstrated dramatically However if the valves associated with muscle pumps are intact and functioning efficiently then considerable retrograde filling from the saphenous opening can be adequately compensated for with consequent maintenance of low pressure in the superficial veins On the other hand retrograde *filling* from the saphenous opening in a patient who has even a minor valvular defect *in the perforating veins is a much more serious* condition The latter group of patients has a double defect in that (1) they have a reduced capacity to return blood to the heart and (2) on walking they actually pump blood at high pressure into the superficial venous grid (Figs 4 7)

It should be obvious therefore that the study of the dynamic limb is more important than the study of the static limb and in order to pick out the cases of serious incompetence it is necessary to measure the pressure in the affected superficial vein in the patient walking as well as standing

This is at present impossible since there is no simple machine which is capable of recording the changes in pressure in the walking patient We would like to stress once more that the assessment of the capacity of the pumps to reduce the pressure in the superficial system is the essential assessment of the abnormality Retrograde filling from the termination of the long saphenous vein can be *compared to* a leaking ship which can remain afloat provided that the capacity of its pumping system is in excess of the leak

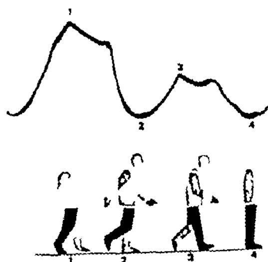


Fig 2 Diagram of walking complex

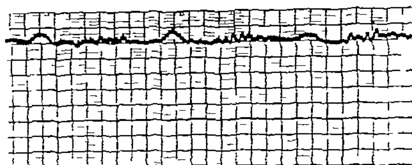


Fig 3 Abnormal pedal trace recorded in the long saphenous vein in the middle third of the leg Incompetent perforating veins are present The base line is three large squares from the bottom and each large square is equivalent to a pressure of 10 mm Hg

Failure to achieve low pressure on walking should be accepted as the essential pathologic feature of the disease This *failure is not directly proportional to the severity of the varicosity but is reflected in the severity of the symptomatology*

We consider that *treatment* should be directed toward the restoration of the efficiency of the pumps by permanently destroying the leaking points rather than to the eradication of superficial tortuous veins which may in themselves not be a very great embarrassment and are in *many cases* capable of reverting to normal appearance and function after the restoration of the normal pattern of pressure

Tortuous varicosities are due mainly to continuously raised intravenous pressure rather than to intermittent high pressure Veins are capable of withstanding high intermittent pressure provided that it is followed by a period of reduced pressure during which they can recover their tone

The cusps of the valves in tortuous veins are often normal and are only incompetent because the diameter of the lumen of the vein has been increased to such an extent that the valve flaps are unable to meet (see Fig 6) When the leaks in the damaged perforating veins are remedied the vicious cycle is broken The tortuous superficial veins relieved of their high pressure return to their normal size and the valves regain their competency It is unnecessary and illogical to strip out veins simply because they are varicose Most of these veins are potentially normal and once the *raised* pressure in them is relieved they may revert to their normal state

The functions of valves are threefold (1) They constitute an essential element of the complex pumping grid (2) They retain the high pressure within the deep system and prevent its transmission to the superficial system (3) They direct the *flow of blood from the superficial to the deep veins*

Valvular incompetence may be of two kinds which we have chosen to call *primary* and *secondary* In primary valvular incompetence valves become involved in fibrous adhesions and can never again function efficiently whereas in secondary incompetence the valve is normal and the incompetence is due to dilatation of the vein It is this secondary type of incompetence that is reversible after the pressure in the superficial veins is returned to a normal pattern after the restoration of the efficiency of the pumping system

Our attention was first drawn to this by observing that saphenous varices disappeared spontaneously after the sclerosis of an incompetent Hunterian perforating vein (Fig 7) We have observed this on *numerous occasions in the last 5 years* Of the 14 000 patients treated by us not one has required the high flush ligation treatment for the relief of symptoms and in the vast majority of cases the dilated tortuous vein above the highest Hunterian perforator has returned to normal

One cannot stress too often the importance of exact diagnosis as a prerequisite to any form of treatment We consider it to be absolutely essential to locate accurately the incompetent perforating veins This is ... done by following a

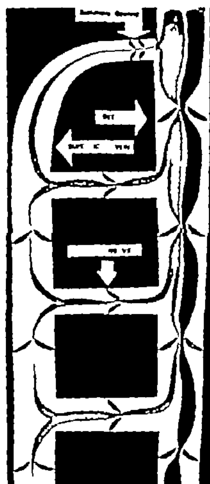


Fig 4 Diagram of normal venous return

diagnostic ritual which we have laid down in our Clinic

The old form of injection treatment produced a painful and uncontrolled thrombus which nine times out of ten recanalized The end result in many cases left the patient worse than before treatment because normal valves became involved in the thrombus and after reopening of the veins these valves were incompetent because of the resulting adhesions

We must now attempt to make clear that our treatment is essentially different from the thrombus produced by the old injection technique The object is to produce a short fibrous cord replacing the superficial vein and involving the perforating vein In order to do this it is necessary to introduce a small amount of sclerosant into the superficial vein which has been emptied by elevation of the leg and to hold it isolated and unmixed with blood for a given period of time at the site of injection This allows chemical necrosis of the intima to take place If this vein is now compressed and maintained in a contracted state for approximately 6 weeks a series of important changes take place An analogy might be made to the revascularization of the head of a femur after avascular necrosis the thrombus and intima are analogous to the head of a femur which has to be revascularized the revascularization extends across the intima and involves the small amount of thrombus which invariably forms in the vein (Fig 6) At the same time fibrous tissue is laid down in the wall of the contracted vein producing an irreversible fixation

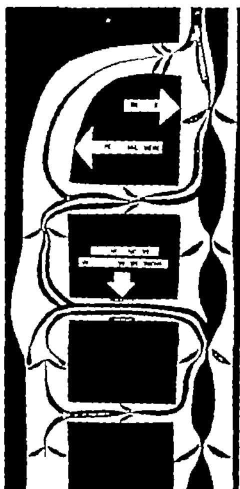


Fig 5 Diagram of venous return in a patient with an incompetent perforating vein but possessing adequate compensation

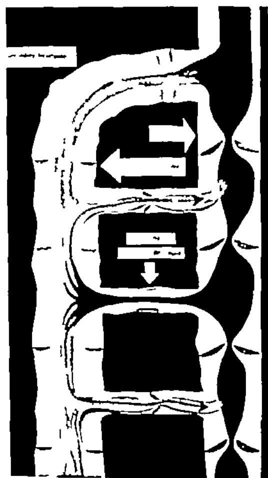


Fig. 6. Diagram of venous return in patient with an incompetent perforating vein with breakdown of compensation. The valves in the superficial veins have become secondarily incompetent. In these cases a dramatic retrograde filling from the saphenous opening can be demonstrated.

The changes that have been observed in sections taken from treated veins at varying intervals after injection are as follows. Changes take place in the vasa vasorum, adventitia, media, subintimal layer, intima, and in the small amount of thrombus in the lumen. There is a marked contrast between the histologic changes in the vein treated by our technique and those in the thrombosed vein which resulted from the old injection technique.

The first comparison is the relative difference in thickness between the wall of the vein and the thrombus within it. In phlebitis the diameter of the thrombus is many times greater than the thickness of the wall of the vein, whereas this proportion may well be reversed when compression is applied immediately after injection. In this case the wall is many times thicker than the thrombus (Fig. 9).

In the cases in which treatment is applied successfully a rich hyperemia from the vasa vasorum is observed. The new blood vessels are seen to grow into the media and can be observed to disrupt the internal elastic lamina at many points, passing through the intima and invading the thrombus.

The intima would appear to allow (1) plasmatic substance from the small thrombus in the vein lumen to pass out into the media separating the muscle fibers

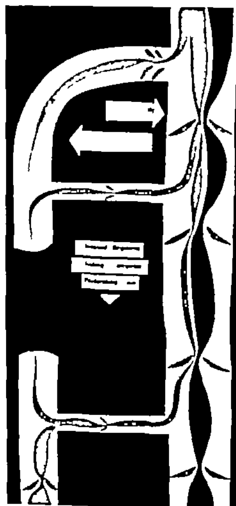


Fig. 7. Diagram of venous return after occlusion of an incompetent perforating vein.

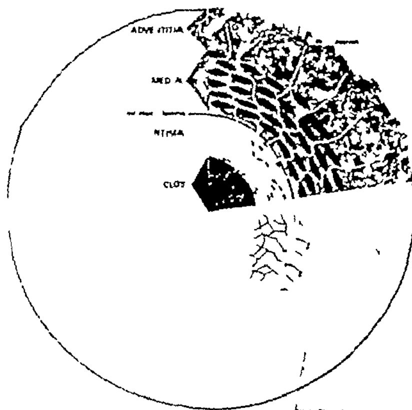


Fig 8 A diagrammatic representation of the analogy between revascularization of an injected vein and an avascular head of femur

and (2) new blood vessels from the vasa vasorum to invade the thrombus Large cells arising in the subintima grow freely in two directions—into the thrombus and in the opposite direction into the media

The large subintimal cells appear to be totipotent They can be observed to act as macrocytes fibroblasts or as a lining for venous sinuses according to necessity Otto Vos in a personal communication has told us that he has found that the concentration of aminoacids surrounding macrocyte cells can influence their behavior His work was done in vitro and helps to explain our findings in vivo

Fibrous tissue is progressively laid down in the media and in the thrombus The capillaries from the vasa vasorum regress and the vein is now replaced by a hard fibrous cord which constitutes a permanent obstruction

Sections taken after thrombosis show a very different picture Many large venous sinuses appear through the thrombus These dilate as the thrombus shrinks and new venous channels are established through the substance of the thrombus This does not happen when the amount of thrombus is minimal and the wall of the vein is thick as after compression There is an inverse relationship between vascularization of the thrombus from the vasa vasorum and the development of venous sinuses within the thrombus The more prolific the vascularization the less likelihood is there of venous sinuses developing and therefore of a new channel forming within the vein The capillaries and venules which develop from the vasa vasorum never establish communication with the venous sinuses but regress after the organization of the thrombus

When advocating the treatment of varicose veins in pregnancy it is often said that we are meddling insomuch as we are treating a condition which four times out of five resolves in the puerperium

This indictment of meddling is refuted on the following grounds (1) If 20 per cent of the patients suffering from varicose veins during pregnancy do not recover in the puerperium then this represents a large number of patients with varicose veins One must make sure that 100 per cent recover In order to do this one must treat *ALL* pregnant women who have varicose veins (2) If patients with varicose veins are not treated during pregnancy it is very likely that the condition will continue to deteriorate past the critical point beyond which recovery in the puerperium is not possible (3) Why should women suffer for months with a condition which is readily amenable to a safe and simple form of treatment (4) The greatest reason for treating varicose veins during pregnancy is the absence of superficial and deep vein thrombosis and pulmonary embolism in the puerperium of patients so treated

In 1952 we took over the responsibility of treating varicose veins in the Rotunda Hospital At that time there was a special clinic which was concerned solely with the treatment of varicose ulcers At the present time there is no patient with varicose ulceration attending the hospital and there has not been for over 4 years In the past 5 years there have been 5 cases of superficial phlebitis during the puerperium in patients treated in our clinic These 5 cases were patients who did not complete their treatment There has been no case of deep vein thrombosis or pulmonary embolism All patients attending the Rotunda Hospital who have varicose veins are referred to this clinic Because of the beneficial effect of prenatal treatment on the puerperal thrombotic complications it is considered that a special clinic such as the one in the Rotunda Hospital should be attached to all large maternity hospitals

Perhaps it appears that this simple technique is easy to perform and that all that is required is to inject a vein and then bandage it but this is incorrect

If 20 house surgeons are invited to perform 20 appendectomies the likelihood will be 100 per cent success but if the same 20 young doctors are invited to apply a bandage which has to stay in position without moving for 6 weeks it would be surprising if the rate of success was more than 50 per cent In these hands the results of our technique would be extremely poor since it is absolutely dependent on the uninterrupted maintenance of adequate compression applied immediately after injection This is difficult to achieve for many reasons (1) the shape of the patient's legs—sometimes tubular and sometimes conical (2) excess adiposity (3) the alteration in the size of the patient's legs due to either swelling or shrinkage and (4) the natural tendency of a bandage to come off the leg of a patient in bed at night

It is essential therefore to become adept at bandaging before commencing this treatment and not to delegate this apparently trivial and unimportant part of the treatment to a subordinate After a short time most young doctors working in our clinic become expert and their results are indistinguishable from our own They must however have the capacity to take infinite care with the simplest details

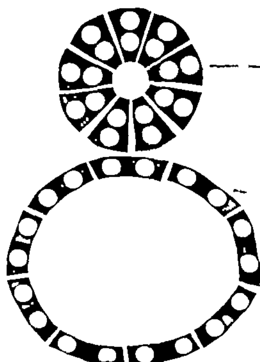


Fig 9 Diagram of the proportions of vein wall to thrombus in compression sclerosis and spontaneous thrombophlebitis

Summary

We should make it clear that we are in no way opposed to the surgical treatment of varicose veins when this implies accurate location of the perforators with their interruption and ligation followed by repair of the fascial orifice transmitting the perforators

We are completely opposed to the old injection therapy which resulted in uncontrolled thrombosis

The inherent advantages of our technique are as follows (1) immediate relief of symptoms (2) absence of mortality and morbidity (3) simplicity of application (4) an outpatient treatment (5) inexpensive (6) avoidance of phlebitis and pulmonary embolism in the puerperium

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Experimental and laboratory reports

Epicardial and intramural excitation in chronic myocardial infarction

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In their classic study of 1935, Wilson and associates[1] concluded after extensive experimental studies on the dog heart that the abnormal Q waves present in epicardial complexes in chronic myocardial infarction are caused by a transmission of left ventricular cavity negativity to the epicardial surface of the infarcted area ("window" theory). From the absence of an appreciable increase in duration of the complexes with abnormal Q followed by a small R wave found in subendocardial infarction, they deduced that the excitatory impulse reaches the endocardial surface of the infarction at the normal time. The transmission of the excitatory wave through the infarcted area was considered to be "a perplexing problem," but intra-infarction conduction by way of strands of surviving muscle was assumed. The broad complexes of the QR type with a duration of 0.12 second or more sometimes found in human myocardial infarction may be caused by a delay in activation of subendocardial muscle by local involvement of the Purkinje system or abnormally slow transmission of excitation through the cardiac muscle.[2]

Other authors have assumed the presence of additional factors responsible for this increase in QRS duration. (a) Contraction of scar tissue resulting in atrophy of surviving fibers which become incapable of transmitting the excitatory wave. Therefore a lamina of normal muscle superjacent to the dead zone and extending to the epicardial surface is activated in tangential direction. The greater distance traveled by the excitatory wave toward the centroid of the infarcted area results in a considerable increase in QRS duration and a deformation of the last 0.04 second portion of the QRS complex.[3] (b) A block in certain parts of the specific conduction pathways of the left ventricle, possibly one of the two main divisions of the left bundle.[4]

According to some authors, infarction confined to inner layers does not change the form of epicardial complexes (silent zone, electrical endocardium).

Some of the factors mentioned above lack experimental evidence. An analysis of epicardial and intramural excitation in chronic myocardial infarction, using techniques described previously,[5] and

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an accurate anatomic-electrocardiographic correlation seemed indicated in order to study (1) the importance of the several factors mentioned in the genesis of the QRS abnormalities and (2) the influence of scars located in the subendocardial layers on the epicardial electrocardiogram.

Methods

In 10 adult mongrel dogs 4 to 10 weeks after ligation of one or two branches of the left coronary artery at the anterior surface, a second left lateral thoracotomy was performed.

The pericardial adhesions caused by the first operation were dissected and an accurate drawing of the epicardial surface was made. For exploration a small tipped electrode was used. To improve post-mortem reconstruction, imaginary lines were drawn parallel to the sulcus atrioventricularis at a distance of about 0.5 cm. and the epicardial points to be explored were spaced along these lines, using intersections with ramifications of the coronary arteries as reference. In every experiment at least 50 epicardial complexes from the infarcted area and surrounding normal muscle were recorded. At selected points on the infarcted area intramural electrodes were introduced. Two different types which gave identical records were used. One type was described previously,[9] the other one of the same dimensions consisted of 10 small isolated wires equally spaced along a central shaft and spirally wound for 360 degrees over a distance of 2 cm. The isolation was removed at one side along the central axis of this structure so that there were small terminals at equal distances of about 2 mm. The surfaces of both types of electrodes were polished carefully because even small irregularities of the surface result in movement artifacts in the records.

Unipolar complexes from and bipolar complexes between consecutive intramural terminals were registered; the polarity of the bipolar complexes was positive if outward spread of the excitatory wave was present. Intramural position was assumed if the intramural bipolar and unipolar complexes showed fast deflections, even of small voltage. These deflections are caused by local excitation, i.e., by depolarization of muscle fibers in contact with the exploring terminals.[11]

In all cases the beginning of the left ventricular cavity complex was used as reference. Intrainfarction conduction was studied during normal and premature beats elicited by stimulation between two adjacent terminals located in the scar.[1] After the experiment was ended the heart and great vessels, together with the intramural electrodes, were removed. The puncture canals were filled with Indian ink, and the intramural electrodes were replaced by broad-tipped needles of the same size. The epicardial surface of the specimen was compared with the drawing and the points explored were indicated with small dots of Indian ink by the same person who made the drawing and applied the exploring electrode. Blood in the cavity was rinsed out with physiologic saline and the heart was suspended in 10 per cent formalin after the ventricular cavities had been filled with cotton wool soaked in the same fluid. After sufficient fixation the heart was cut into slices along the imaginary lines parallel with the atrioventricular sulcus. Microscopic sections of 7μ thickness were made and stained alternatively with hematoxylin eosin and Van Gieson. In most cases it was possible to include the puncture canal in one section.

In three instances the heart with scar was removed immediately after operation and perfused according to Langendorff with a 3½ per cent hemoglobin solution. The endocardial surface of the scar and adjacent normal tissue were explored by long electrodes which were introduced through the apex and which had at their tips two small terminals at a distance of 1 mm. Unipolar leads and close bipolar leads were used.

Results

I. Normal epicardial and intramural excitation. The beginning of epicardial complexes recorded under experimental conditions similar to those during exploration of the infarcted hearts was nearly always synchronous with the beginning of the cavity complex. The Q wave, if present, had a duration up to 14 msec., the nadir occurred at 4 to 10 msec., and the voltage

was 3 mV or less. At the region near the atrioventricular sulcus these values were respectively 18 msec, 14 msec and 4mV. At some places, mainly at the left side of the anterior attachment of the ventricular septum and at the apical anterolateral region, a small positivity or small deflection in the descending limb of the q wave preceded the high R wave, giving rise to a qrs Rs form. The nadir of the small q wave occurred at 7 or 8 msec, rarely at 10 msec; the small r wave occurred at 11 to 17 msec, and the nadir of the s wave coincided within a few milliseconds with the nadir of the cavity complex, 19 to 21 msec.

II. Epicardial excitation in myocardial infarction. Several characteristics were common to all myocardial infarctions independent of the degree of intramural extension. (1) The area with abnormal Q waves was always slightly larger than the infarcted area. At some places a difference of about .5 cm was found. (2) The beginning of Q and the beginning of the left ventricular cavity potential were synchronous. (3) There was a delay in excitation of the epicardial surface of the infarcted area, except in the case of subendocardial infarction with small intramural extension.

A. SUBENDOCARDIAL INFARCTION. All epicardial complexes from points overlying subendocardial scars were abnormal. Even the smallest infarction in our series with the largest diameter of less than 1 cm and an intramural extension of less than one fourth of the thickness of the ventricular wall showed abnormal Q waves. With small intramural extension (Fig. 1) only the initial part of the depolarization complex was changed, and broadening of the Q wave occurred, with a slight increase in depth (4 mV or more) and nadir distance (11 msec or more). With larger intramural extension the duration and depth of the Q wave increased. After about 13 or 14 msec the slope of the descending limb increased rather sharply. The R wave often had a slow downstroke.

Epicardial excitation times of infarctions of the former type all fell within normal limits and no changes in the excitation pattern were found.

The pattern of epicardial excitation in hearts with greater intramural extension of the scar can be seen in Fig. 2. The central parts of the infarcted area were activated later than the lateral parts at the same level, the area of latest activation lay at the basal region. Here values up to 50 msec were present. In this instance the lateral side of this basal area was bordered by an area with normal excitation time; the difference between these closely adjacent regions was 15 msec.

B. TRANSMURAL MYOCARDIAL INFARCTION. Only at those places where the infarction was transmural were QS complexes present, often with notching of both limbs which sometimes occurred even after the end of the QS complexes. These small deflections were synchronous with the rapid deflections recorded with close bipolar leads from the same place.[1] There may be great variations in form of the unipolar epicardial complexes, even in a small area, if large differences in anatomic structure of the subepicardial layers are present.

At a small zone of the surface around a transmural infarction abnormal Q waves were found; however, the inner layers were intact.

III. Analysis of intramural infarction. A. SUBENDOCARDIAL INFARCTION. In every instance unipolar complexes from the intrainfarction terminals had a QS

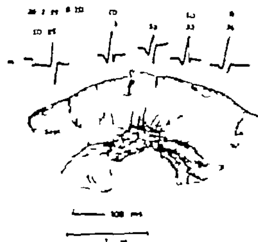


Fig. 1. Subendocardial infarction with small intramural extension. The [illegible] broadening and an increase in the depth of the Q wave. Epicardial excitation is not delayed.

form. With larger intramural extension the number of terminals which showed this type of complex increased. The complexes from terminals situated between scar and epicardial surface had embryonic R waves gradually increasing in size and with progressively later time of onset of the intrinsic deflections.

The bipolar complexes of the infarcted area had a low voltage and were notched. The time relationships of these small rapid deflections occurring at consecutive terminals were often compatible with a predominant outward spread of these waves (Fig. 4).

Those from the normal outer layers were of normal voltage, but broadening may be present.

In all instances of subendocardial infarction confined to a small zone microscopic examination of the scar revealed the presence of fibrous tissue with strands of muscle fibers reaching the puncture canal.

With larger intramural extension the scar sometimes consisted in large part of dense fibrous tissue, a small layer of muscle being present near the epicardium. The unipolar complexes from these parts of the scar had a QS form with smooth limbs. Those from the superjacent muscle had a QR form with nearly synchronous downstrokes of the intrinsic deflections and of the rapid parts in the bipolar complexes (Fig. 5).

Epicardial excitation times of this layer were consistent with activation in a tangential direction more or less parallel with the epicardial surface.

This situation is illustrated in Fig. 6 as indicated by the gradual increase in epicardial excitation times of complexes 1 ± 4. The scar consisted of dense fibrous tissue only. A comparison of complexes 4 and 5 will reveal the influence of excitation of the outer layers on the epicardial R wave. A strand of fibrous tissue separates an area activated early from one showing late activation.

B. TRANSMURAL INFARCTION. Intramural unipolar complexes from a transmural infarction all have a QS form (Fig. 3). The beginning and nadir of these complexes are synchronous with corresponding parts of the cavity complex. If viable muscle fibers were present, the bipolar complexes of small voltage were broad and showed many notches (Fig. 7A). Large differences in time relationships of the intrainfarction excitation waves at consecutive terminals may be present (Fig. 7B). If the scar was deprived of muscle fibers broad smooth bipolar complexes of low voltage were recorded (Fig. 3).

C. INTRAINFARCTION CONDUCTION DURING PREMATURE BEATS. The form of the bipolar complexes during normal beats was compared with that of complexes caused by stimulation of endocardial terminals situated in and around the infarcted area. Sometimes gross changes occurred (Fig. 8); in other instances there was a larger degree of correspondence between bipolar complexes from normal and from premature beats.

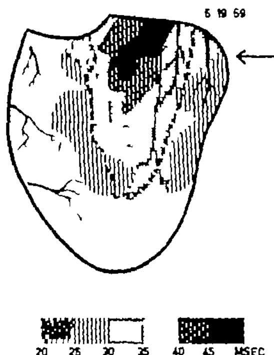


Fig. 2. Epicardial excitation in infarction of inner half of a part of the left ventricular wall. In the apical half intrainfarction conduction was demonstrated but not in the basal region where no muscle fibers were present in the scar. In this region two areas lying close together showed large differences in the time of arrival of excitation. Tangential activation was found in the muscle overlying this part of the scar (arrow). The centroid of the scar is activated late. The boundary of the greatest extension of the dense part of the infarcted area is indicated by the broken line. The arrow indicates the site of the section shown in Fig. 6.

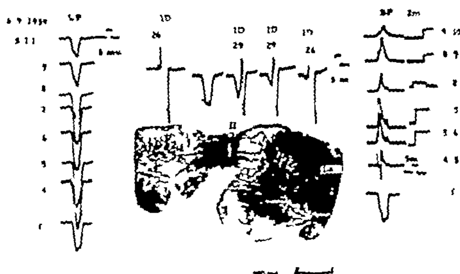


Fig 3 QS complexes are found at that part of the epicardial surface where the infarction is transmural The intramural electrode was introduced obliquely into the ventricular wall Only a part of the puncture canal is visible QS complexes are recorded throughout the infarcted area (5 6 7) At terminal 4 a Purkinje spike occurring 4 msec after the beginning of the cavity complex is present and also visible in bipolar complex 4-5 No surviving intrainfarction fibers were present The bipolar complexes (BP) have a low voltage and are smooth

D PERI INFARCTION CONDUCTION If the intramural electrode was situated in normal muscle that bordered on the scar the intramural complexes had a normal form but the intrinsic deflections at the consecutive terminals occurred later than normal The bipolar complexes were broad but had a normal form Average conduction velocity of the intramural excitation wave was reduced with 20 cm per second being the lowest value found

E PURKINJE ACTIVATION In one experiment the intramural terminals 1 to 5 were in contact with the anterior papillary muscle which showed diffuse fibrosis of its basal half At these terminals Purkinje spikes were present occurring 0 to 5 msec after reference Purkinje spikes were also recorded from the endocardial surface of the infarcted area in isolated dog hearts In these instances too they nearly all occurred within this interval only one spike was recorded 9 msec after reference

F IVALON INFARCTIONS In three experiments a part of the left ventricular wall was replaced by Ivalon sponge and after 4 to 6 weeks an intramural electrode was introduced into the center of this Ivalon mass The bipolar complexes (Fig 9) were broad and of small voltage The unipolar epicardial complexes had a very unusual form

Discussion

The genesis of the changes caused in the epicardial complexes by myocardial scars can be demonstrated by comparing the unipolar complexes recorded from the consecutive intramural terminals of the infarcted part of the ventricular wall

Unipolar complexes

A SUBENDOCARDIAL INFARCTION In subendocardial infarction with small intramural extension QS complexes are recorded from terminals located in the infarcted area If small notches are present they are caused by depolarization of the muscle fibers in contact with subendocardial terminals The Purkinje spikes recorded in the subendocardial zone of the scar all fell within normal limits R waves increasing in size toward the epicardial surface are found in normal tissue between infarction and adjacent epicardial surface caused by the outward spreading excitation wave in this layer Conducti

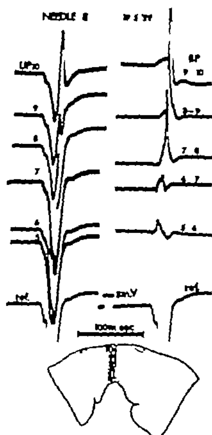


Fig. 4. The unipolar complexes of terminals 5, 6 and 7 situated at the lateral part of a subendocardial scar have a QS complex. The unipolar complex of terminal 8 situated in normal muscle has an embryonic R wave gradually increasing in size in complexes from terminals situated closer to the epicardial surface. Bipolar complexes 5-6 and 6-7 are small and notched. There is a time difference of 10 msec. between their tops. Probably outward spread is present. Conduction velocity in the outer layers is reduced (30 cm. per second).

velocity is diminished. Values of 20 to 30 cm. per second were encountered. The abnormalities caused by the loss of subendocardial tissue are transmitted toward the epicardial surface. In scars which have deeper intramural extension and which consist of fibrous tissue only, the intact muscle between scar and epicardium may be activated in a tangential direction as indicated by the time of occurrence of the intrinsic deflections and identical QR form of the intramural complexes.

B. TRANSMURAL INFARCTION. Unipolar complexes from all layers of the infarcted area show nearly the same QS pattern as the cavity complex, the voltage decreasing slightly toward the epicardial surface. There is an unopposed transmission of cavity potential through the wall toward the epicardial surface as postulated by Wilson and associates.

If the infarction is completely deprived of muscular tissue, the QS complexes are smooth. If the intramural terminals are in contact with strands of surviving muscle fibers, notches on both limbs are present.

In some instances, depolarization of muscle fibers occurred even after completion of the QS complex. The largest value found was 30 msec.

Bipolar complexes. The intramural bipolar complexes recorded throughout the scar are grossly changed; the main features are the loss of voltage, increase in duration, and sometimes excessive notching. The voltage is reduced because of the partial or complete loss of depolarizing tissue. Cancellation is often an additional factor because multiple excitatory waves may be present in the infarcted area. The import-

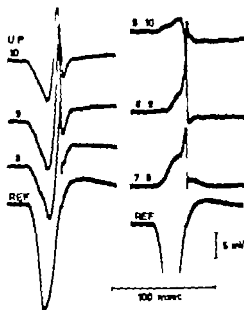


Fig. 5. Unipolar and bipolar complexes from a subendocardial infarction without surviving muscle fibers. The terminals 8, 9 and 10 were situated in the normal ventricular muscle between scar and epicardium. The unipolar complexes are very similar. The intrinsic deflections in these complexes and the rapid parts in the bipolar complexes occur nearly synchronously. This is an example of tangential activation.

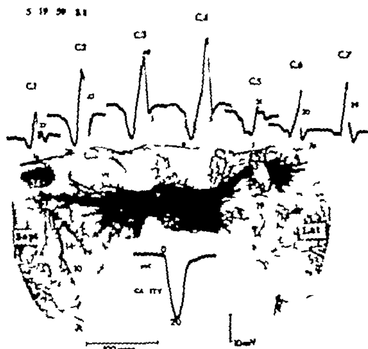


Fig 4 The [illegible] of thi section indicated b the arrow n Fig 2 Den-e ubendocardial infar tion w thout intrainfarction muscle fiber The figures near the epicardial complexe indicate the time of oc urren e of the rapid part of the intrin ic deflection or if absent the beginning and end of the R w e Tangential excitation present progressing toward the ma s of fibrous ti sue reaching the epicardial surfa e A comparison of complexe 4 and 5 demon trates the influence of exci tation of the outer layers on the form of the epicardial R wa The nadir of the Q wa e in complexes 1 ± 4 i synchronous w th the ca ty nadir (20 msec) The figures along the pi ncture canal indicate the time of occurrence of excitation at the intramural terminals The Q wa es of 6 and 7 situated above intact inner and middle layers are abnormal but gradual filling up is caused by excitation of normal inner layers

ance of this can be judged from the changes in the form of bipolar complexes after stimulation of subendocardial terminals in the scarred zone Sometimes a surprisingly large increase in voltage of these bipolar complexes occurs

The broad smooth bipolar complexes of small voltage found even in a scar completely deprived of muscle fibers and also found inside a mass of Ivalon sponge are not easily explained If septal forces contribute largely to cavity negativity the greater distance of the consecutive terminals should result in a gradual decrease in negativity in unipolar complexes and therefore in small positive waves in bipolar complexes

Intrainfarction excitation The increased duration of the bipolar complexes is caused by a diminished mean conduction velocity of the excitatory waves as can be deduced from the large differences in time of arrival of excitatory waves between consecutive terminals during premature beats elicited by stimulation of intrainfarction terminals This reduction in conduction velocity is not uniform throughout the infarcted area The reasons for this decrease are unknown Our experimental conditions did not allow us to evaluate the role of intrinsic changes in the electrical properties of the intrainfarction muscle fibers It is very likely however that the changed anatomic structure enhances the occurrence of cir

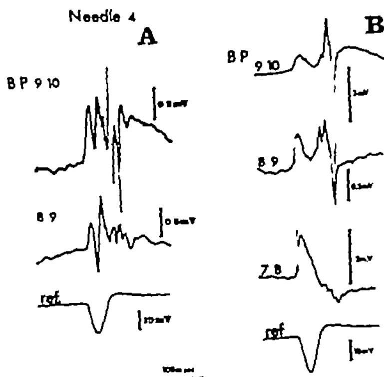


Fig. 7. Bipolar complexes from two intramural electrodes situated in a transmural infarction. A, Broad highly notched complexes. The rapid deflections in 9-10 which occur after the QS complexes of the reference are caused by excitation of muscle in contact with terminal 10. The smooth deflections at the beginning are probably extrinsic phenomena. B, The rapid small deflection in complex 7-8 is caused by excitation of muscle in contact with terminal 8. The same deflection which occurs near the end of the complexes between 9 and 10 is caused by excitation of muscle near 10. The time difference is about 60 msec. The distance between terminals 8 and 10 is 4 mm.

cuitous routes of the intrainfarction excitatory waves resulting in a longer presence of excitation waves between two intramural terminals. This prolongation of excitation may be present in all layers of the scar, even in the subendocardial layers. Notching of the complexes is caused by the desynchronized excitation of the muscle fibers in contact with the exploring terminals.[15]

The circuitous routes make it impossible to map intrainfarction excitation. Moreover, the presence of time relationships compatible with an excitatory wave progressing in a certain direction does not necessarily prove the existence of such an excitatory wave. The highly intricate topography of the infarction may probably under certain conditions simulate such a temporal sequence. Sometimes it could be made plausible, however, that the excitatory wave originated from the subendocardial regions of the infarcted area. Then the form of complexes from normal beats and from premature beats caused by stimulation of subendocardial terminals in the infarcted area showed a large degree of correspondence.

Peri-infarction excitation. A thin muscle layer overlying a scar devoid of muscle fibers shows excitation nearly parallel with that of the epicardial surface. The time relationships indicate the presence of a reduced conduction velocity. This finding is the experimental verification of peri-infarction block as postulated by

Bayley The R wave registered from the epicardial surface of this layer was large because during excitation in a tangential direction the excitatory forces in the remainder of the ventricles were reduced or even absent In some instances it was demonstrated that conduction velocity in the apparently normal muscle surrounding the intramural borders of the scar was diminished

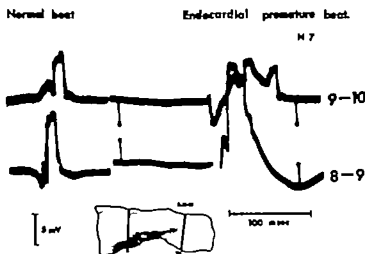


Fig 8 The intramural electrode went through the lateral part of the scar During normal beats broad notched complexes were present these broadened during stimulation of terminal situated in the intact inner layers

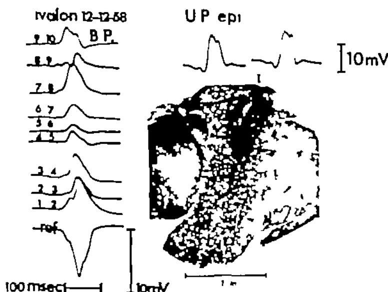


Fig 9 A part of the left ventricular wall was replaced by ... of ... The bipolar complexes recorded from its center reveal broad complexes of small voltage The epicardial complexes have unusual form and are possibly caused by peri infarction block

Epicardial complexes in myocardial scars The presence of subendocardial scars even with small intramural extension resulted in abnormal Q waves in every instance The small initial deflections which at some places precede the R wave disappear Conversely if the initial part was normal the subendocardial layers were intact The abnormal Q wave is caused by loss of depolarizing subendocardial tissue except at the small transition zone bordering the scar where the complexes show a gradual change toward normal The abnormalities visible in the initial part of the epicardial QRS complex could be recorded from the intramural terminals situated between scar and epicardium We could find no explanation for the sudden increase in steepness of Q which occurred after 10 to 14 msec

No evidence for a delay in excitation of preserved subendocardial Purkinje fibers at the infarcted area was found even in isolated hearts in which a careful exploration of the endocardial surface was possible Therefore a condition fulfilling the criteria for arborization block[12] was not encountered

In our experiments no silent zone was found In that part of the normal left ventricle in which all infarctions were made depolarization of the inner layers may cause a small positive deflection in the unipolar epicardial complexes preceding a large R wave (qrs RS type) or situated at the beginning of the ascending limb of the R wave sometimes separated from this deflection by a notch This indicates that density and degree of intramural Purkinje penetration are not sufficient to result in such a degree of cancellation of the excitation wave that these inner layers are silent in so far as epicardial leads are concerned

There is however a smaller influence of excitation of the inner layers on epicardial complexes due to several factors (1) occurrence of depolarization during the phase of rapidly increasing negativity of cavity potential[1] (2) a certain degree of intramural penetration of Purkinje fibers at many sites on the apical half of the anterolateral part of the left ventricular wall which results in the occurrence of QS complexes in unipolar complexes from terminals situated in these layers (3) the trabeculated structure of inner layers which increases cancellation of the excitatory waves present in these layers and (4) the large distance in relation to the exploring epicardial electrode

Epicardial excitation In small subendocardial infarctions no delay in epicardial excitation could be demonstrated Comparison however with the preinfarction values was impossible because of the altered anatomy of the epicardial surface at the time of the second operation The points explored therefore could not be retraced In subendocardial infarctions of larger size epicardial excitation is profoundly changed its delay is marked The centroid of the subepicardial muscle overlying the infarction is activated late there is inward spread at many places Sometimes two closely adjacent regions show large time differences these differences are caused by fibrous tissue strands which prevent the propagation of excitation from the area activated early The epicardial surface which borders the infarcted zone is activated without demonstrable delay

In transmural infarction the small remnants of living muscle found at the epicardial surface are activated late sometimes 30 msec after the QRS complex The bizarre complexes sometimes encountered in close bipolar complexes remained constant from beat to beat

Proximity potential The epicardial complexes reveal the presence of even small subendocardial scars The close correspondence between abnormal Q area and anatomic boundary of the scar is evidence that under our experimental conditions there is sufficient local effect of the inner layers on unipolar epicardial leads to allow detection and localization of even small scars Large differences in the form of epicardial complexes from closely adjacent regions in an area with great differences in anatomic structure prove that this proximity effect in so far as the excitation pattern of the subepicardial layer is concerned is even surprisingly large

Genesis of QRS prolongation The prolongation of QRS is caused by the diminished conduction velocity of the intrainfarction and the peri infarction muscle

fibers and circuitous spread of excitation through the preserved myocardial cells. The first factor is partially balanced by a decrease in the thickness of the infarcted part. If intrainfarction conduction is absent, excitation from the peri-infarction muscle is present solely. The epicardial complexes of the Ivalon mass are probably explained by peri-infarction block only.

In view of the fact that several factors may be responsible for the occurrence of an increase in QRS duration after infarction and in many instances peri-infarction block may be only one of them, the term *postinfarction block* should be used.[16]

Summary

Epicardial and intramural excitation patterns were studied in 10 dogs with myocardial scars of different size and location produced by occluding a branch of a coronary artery 4 to 10 weeks prior to the experiments.

Even the smallest subendocardial scar present in our series, with the largest diameter of nearly 1 cm and intramural extension of less than one fourth of the thickness of the left ventricular wall, resulted in the occurrence of abnormal Q waves in unipolar epicardial complexes. Under our experimental conditions a close correspondence existed between anatomic extension of the scar and epicardial area showing Q abnormalities, the latter was often slightly larger. We found no evidence for the existence of a silent zone.

In infarction the cavity complex is transmitted through the infarcted area toward the epicardial surface.

The main reason for the abnormal Q wave in subendocardial infarction is the loss of voltage. There is no delay in excitation of the Purkinje fibers at the endocardial surface of the scar. An arborization block was not present. Living intrainfarction muscle fibers are responsible for the transmission of excitation but intrainfarction excitatory waves follow circuitous routes. The time differences in local excitation between consecutive terminals may be very large. Mean conduction velocity is reduced (intrainfarction block).

Evidence is given that in some instances excitation reaches the scar from the endocardial surface and progresses through the infarcted area toward the epicardial surface. In the normal muscle surrounding the myocardial infarction the conduction velocity of the excitatory wave may be reduced (peri-infarction block). If the scar is devoid of muscle fibers the excitatory wave reaches the epicardial surface by way of these fibers. A small layer of muscle superjacent to a large scar may generate a large and late R wave. Conduction in a tangential direction has been found.

Because intrainfarction and peri-infarction block may be present to a varying degree, the term *postinfarction block* should be used.

The epicardial surface of a scar is activated late except in the case of very small subendocardial scars. Adjacent areas on the epicardial surface may show large differences in time of arrival of the excitatory wave because of the presence of intramural fibrous strands reaching the epicardial surface and separating these areas.

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I Effects of perfusion of oxygenated micromolecular solutions at normal atmospheric pressure into the ischemic left ventricular myocardium

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In previous reports we described the ability of fluids of low molecular weight such as glucose or Urographin and higher molecular weight such as dextran (Rheomacrodex, molecular weight of 40,000), hemoglobin, and even plain blood to pass across the myocardial capillary wall and to enter the regional veins when perfused into the ventricular myocardium of the beating or nonbeating heart.[1] Perfusion of fluorescein diluted in dextran into any region of the ventricular myocardium caused the whole heart to become fluorescent. On the other hand, perfusion of dextran of 40,000 molecular weight at a rate of 4 ml. per minute into the ischemic left ventricular myocardium did not significantly alter the heart rate and could restore left atrial pressure and arterial pressure to nearly normal.[14] Better results could perhaps be obtained if isotonic solutions of fluids containing substances of much less molecular weight, such as 5 per cent glucose in water (molecular weight of 180) or Tyrode solution (molecular weight of ± 50) containing oxygen dissolved at 1 or 3 atmospheres absolute (3 ATA) could be perfused into the ischemic myocardium.

The absence of any information in the literature about the effects of intramyocardial perfusion raises several questions which require further evaluation before the effects of intramyocardial perfusions in the ischemic myocardium can be studied.

The first question to decide is *what sort of micromolecular solution* lends itself best to perfusion. Isotonic glucose in water oxygenated at 1 or 3 ATA is known to cause ventricular fibrillation when perfused into the coronary arteries.[8] In previous experiments, we have demonstrated that perfusion of Tyrode solution into a main coronary artery could maintain the heart function and pressures until anemia due to exsanguination occurred.[8]

With Tyrode solution having been selected for the intramyocardial perfusion, the next questions to be answered are these: (a) What *amount of Tyrode solution* should be perfused? (b) What is the *most suitable myocardial area* for perfusion?

Perfusion of Tyrode solution at a rate of 2 ml. per minute for 60 minutes into three different regions of the normal myocardium of 12 dogs was well tolerated. Extrasystoles and a small decrease in arterial pressure and an increase in the left ventricular end diastolic pressure occurred when the perfusion was performed into the anterior medioventricular region or left border of the left ventricular myocardium. The cardiac output (determined

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by the dye dilution technique) was reduced to about 14 per cent When the apex was perfused the pressures and cardiac output remained at about the same level

On the basis of the foregoing indispensable preliminary information the perfusion of the ischemic myocardium could be experimentally evaluated by perfusion of oxygenated Tyrode solution at 1 or 3 atmospheres absolute pressure into the ischemic left ventricular myocardium after occlusion of (1) the anterior descending coronary artery and (2) the circumflex coronary artery

Perfusion of oxygenated or nonoxygenated Tyrode solution at 1 ATA into the ischemic left ventricular myocardium

A Perfusion into the anterior surface of the ischemic ventricular myocardium after occlusion of the anterior descending coronary artery

METHODS Thirty mongrel dogs which weighed between 14 and 17 5 kilograms were used Anesthesia was induced and maintained with intravenous Nembutal 25 mg per kilogram The animals were ventilated with 100 per cent oxygen The chest was opened widely as previously described [10] Special care was taken to keep the temperature stable with a heating lamp [9] Pressures arterial venous and left ventricular end-diastolic (LVEDP) from a catheter inserted through a femoral artery and electrocardiograms were recorded Cardiac output (CO) was continuously determined by the dye-dilution technique The anterior descending coronary artery was then prepared and occluded 1 cm distal of its origin Care was taken that the septal artery remained unobstructed Thirty minutes after coronary occlusion a No 18 Rochester plastic needle was inserted into four myocardial regions (1) the center of the cyanotic region of the anterior surface of the left ventricle in the first group of 6 dogs (2) the boundary zone between the cyanotic and noncyanotic regions of the left border of the anterior surface of the left ventricle in a second group of 6 dogs (3) the normal nonischemic myocardium 3 cm left lateral of the former region in a third group of 6 dogs (Fig 1) (4) the anterior surface of the apex of the left ventricular myocardium in a fourth group of 12 dogs (Fig 2)

One to 2 minutes after insertion of the needle perfusion of Tyrode solution was started and adjusted to a rate of 2 ml per minute for 15 minutes after which the perfusion was stopped for 30 minutes In cases in which the arterial pressure had not been increased and the LVEDP had not been decreased to near the preocclusive level the perfusion was repeated for 15 minutes more

One hour later the animals were sacrificed In each second dog the perfused Tyrode solution was bubbled for 1 hour before and during perfusion with oxygen by a technique described before [9]

RESULTS For a few seconds to 1 minute after occlusion of the coronary artery the anterior wall of the left ventricle became blue in color The limits of the changes in color were well demarcated Although the extent of the cyanotic area was variable the anterior surface of the apex was invariably cyanotic During the first 30 minutes of coronary occlusion ventricular fibrillation occurred in 4 animals Through institution of heart massage and defibrillation the heartbeat was restored However the arterial pressures remained at low levels and the LVEDP at high levels As for the other 26 dogs the systemic arterial pressure and the LVEDP remained unchanged in 7 or when changed returned spontaneously to about the preocclusive level prevailing at that time The venous pressure was slightly increased In 19 dogs the arterial pressure and CO were decreased and the LVEDP and venous pressures were increased (Table I)

1 Perfusion into the middle of the cyanotic region of the anterior surface of the left ventricle (a) When after coronary occlusion the pressures remained unchanged perfusion of oxygenated or nonoxygenated Tyrode solution decreased the arterial pressure and CO and increased the LVEDP During the next 30 minutes of nonperfusion the arterial pressures and CO increased to levels slightly below the previous ones and the LVEDP decreased Reperfusion of Tyrode solution after 30 minutes had the same results (b) When after coronary occlusion ventricular fibrillation occurred and after successful defibrillation the arterial pressures and CO were maintained at low levels perfusion

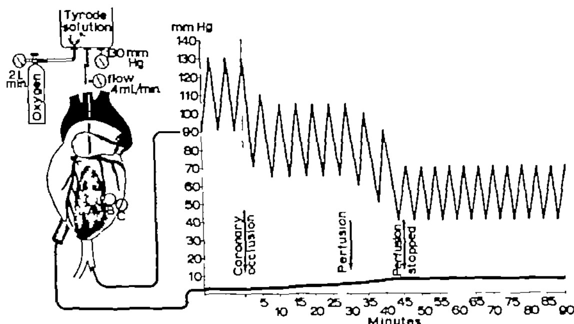


Fig. 1. Hemodynamic changes after occlusion of the anterior descending coronary artery and perfusion of Tyrode solution oxygenated at normal atmospheric pressure into (A) the center of the cyanotic region of the anterior surface of the left ventricle (B) the boundary zone between the cyanotic and noncyanotic region of the left border of the anterior surface of the left ventricle (C) the nonischemic myocardium left lateral from the left border of the cyanotic region

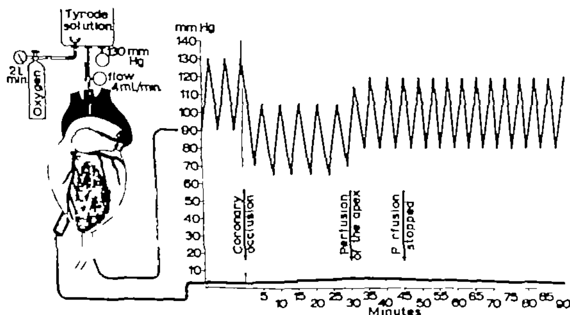


Fig. 2. Hemodynamic change after occlusion of the anterior descending coronary artery and perfusion of Tyrode solution oxygenated at normal atmospheric pressure into the cyanotic apical region

of both types of Tyrode solution decreased the arterial pressures and CO still more. During the second perfusion ventricular fibrillation reoccurred. (c) When after coronary occlusion the pressures were decreased, perfusion of Tyrode solution oxygenated or not increased the extrasystoles and decreased the arterial pressure and CO still more and increased the LVEDP and venous pressures. During the 30 minutes after perfusion the systemic *pressures increased to the previous post-occlusive levels* or remained unchanged (Fig. 3, *1, 2, 3*).

During the second perfusion time the arterial pressure and CO in all animals decreased. The LVEDP and the venous pressure increased. Ventricular fibrillation occurred in one dog. Thirty minutes after the perfusions samples of tissue weighing 1 Gm. each were collected from the perfused ischemic and nonischemic areas. The samples were frozen immediately and homogenized and the tissue levels of lactic acid (milligrams per cent) were determined (by the method of Holhorst). The lactic acid concentration of the nonischemic tissues was between 14.9 and 15.2 milligrams per cent, that of the ischemic tissues 21.2 and 24.4, and that of the perfused ischemic areas 9.8 to 10.4.

2. Perfusion into the boundary zone between cyanotic and noncyanotic myocardium. (a) When after coronary occlusion the pressures remained unchanged, perfusion of oxygenated or nonoxygenated Tyrode solution decreased the arterial pressure and CO and increased the LVEDP. When the perfusion was stopped, the arterial pressures were increased to about the previous level and the LVEDP decreased. After reperfusion the arterial pressure and CO again decreased in all animals and the LVEDP and venous pressure increased. When the perfusion was stopped, the arterial pressures and CO remained unchanged. (b) When after coronary occlusion the arterial pressure decreased, perfusion of Tyrode solution decreased the arterial pressures and CO still more and the LVEDP increased. During the 30 minutes that the perfusion was stopped, the pressures and CO either remained unchanged or increased slightly (Fig. 3, *4, 5, 6*). The LVEDP decreased and the CO increased slightly. After reperfusion the same hemodynamic changes occurred in all animals.

3. Perfusion of the nonischemic myocardium 3 cm. left lateral from the ischemic myocardium produced results simi

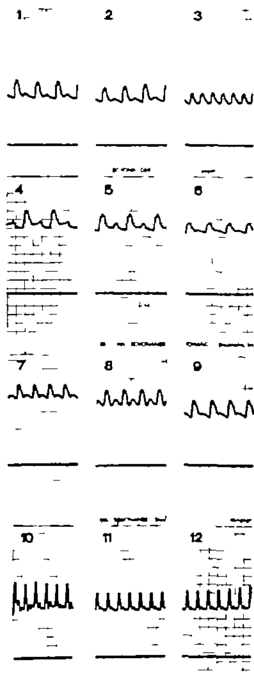


Fig. 3. *1, 4, 7, 10*, Normal arterial pressure after the chest was opened. *2, 5, 8, 11*, Pressure after coronary occlusion. *3, 6, 9, 12*, After perfusion.

Table 1 Hemodynamic changes and cardiac output after perfusion of oxygenated or nonoxygenated Tyrode solution at normal atmospheric pressure into several regions of the anterior surface of the ischemic left ventricular myocardium after occlusion of the anterior descending coronary artery

Dog No	Perfused region				Tyrode solution		Arterial pressure (mm Hg)				LVEDP (cm H_2O)			CO (L/min)			Remarks
	Center cyanotic region	Boundary zone	Non-cyanotic region	Cyanotic apical region	Oxygenated	Non-oxygenated	Before coronary occlusion	After coronary occlusion	After perfusion	30 min after reperfusion	Before coronary occlusion	After coronary occlusion	After perfusion	Before coronary occlusion	After coronary occlusion	After perfusion	
1	+				+		130/100	100/70	80/50	80/50	2.5	3.5	4.5	1.80	1.60	1.40	Fibrillation recurred
2	+					+	110/70	Ventricular fibrillation	70/40	40/70	1.0	4.5	6.5	1.90	1.30	1.00	
3	+				+		140/110	105/70	75/50	115/70	3.0	4.0	5.0	1.40	1.20	1.00	
4	+					+	135/115	125/100	105/80	125/100	0.5	1.0	2.0	1.40	1.30	1.10	
5	+				+		140/100	140/100	115/85	140/100	2.0	4.0	5.0	1.90	1.60	1.50	
6	+					+	125/90	100/ 0	80/60	100/70	0.5	1.0	1.0	1.15	1.05	1.00	
7		+			+		120/80	90/60	80/60	80/60	1.5	2.5	3.0	0.90	0.70	0.60	
8		+				+	125/90	125/90	100/ 0	125/90	3.5	4.5	6.0	2.00	1.60	1.30	
9		+			+		140/110	120/90	100/70	110/90	1.0	1.5	1.5	1.90	1.60	1.60	
10		+				+	125/85	100/30	90/70	100/80	2.5	3.0	4.0	1.60	1.40	1.25	
11		+			+		110/60	90/70	70/50	85/65	1.5	3.0	3.5	1.05	0.98	0.90	
12		+				+	155/110	140/100	120/50	130/90	0.5	1.0	1.5	2.00	1.95	1.90	
13			+		+		150/110	150/110	130/70	115/70	6.0	7.0	7.0	1.80	1.65	1.60	Fibrillation recurred
14			+			+	110/ 5	Ventricular fibrillation	60/30	30/10	2.0	4.0	7.0	1.50	0.80	0.30	
15			+		+		120/60	100/60	0/50	90/60	0.0	0.5	1.0	0.90	0.80	0.75	
16			+			+	140/100	170/90	85/90	100/70	1.0	1.5	2.0	1.60	1.40	1.20	
17			+		+		125/80	115/70	105/60	110/ 0	0.5	1.0	1.0	1.10	1.00	0.90	Fibrillation recurred
18			+			+	130/100	Ventricular fibrillation	90/ 0	40/20	2.0	5.0	7.5	1.70	0.60	0.40	
19				+	+		160/100	160/100	145/80	160/80	1.3	1.0	1.0	2.00	1.90	1.80	
20				+		+	170/80	85/60	105/70	105/70	1.4	1.6	1.8	2.00	1.50	1.40	
21				+	+		140/100	105/75	125/90	125/90	2.5	3.0	1.5	1.44	1.40	1.35	
22				+		+	140/100	140/100	175/80	140/100	1.5	3.0	3.5	1.0	1.50	1.40	
23				+	+		125/95	115/85	170/55	120/85	2.5	3.5	4.0	1.80	1.50	1.50	
24				+		+	170/80	Ventricular fibrillation	60/35	100/60	1.0	5.0	6.0	1.80	0.60	0.50	
25				+	+		140/100	105/75	1 5/90	105/90	3.5	4.0	4.5	1.10	1.00	0.90	
26				+		+	130/95	110/90	170/90	120/90	2.3	2.5	1.0	1.50	1.40	1.20	
27				+	+		150/100	130/80	135/95	135/93		—	—	—		—	
28				+		+	1 0/120	170/100	160/100	170/110		—		—		—	
29				+	+		120/80	100/60	110/60	110/70		—	—	—	—	—	
30				+		+	130/90	120/80	115/ 0	130/90	1.5	2.0	2.5	1.70	1.40	1.40	

lar to those in the previous group (Figs 3 7 8 9 Table I)

4 Perfusion into the apex (a) When after coronary occlusion the pressures were unchanged perfusion of the apex decreased the arterial pressures and CO and increased the LVEDP and venous pressures When the perfusion was stopped the pressures returned to about the previous postocclusive levels within 2 to 6 minutes The CO remained slightly decreased After a second perfusion the same hemodynamic changes occurred (b) When after coronary occlusion ventricular fibrillation occurred and after defibrillation the pressures and CO were maintained at low levels the arterial pressures and CO decreased still more and the LVEDP and venous pressure increased during perfusion (c) When after coronary occlusion the pressures decreased perfusion increased the arterial pressures and CO in all the animals within 5 to 8 minutes to levels slightly under those before occlusion and decreased the LVEDP During the 30 minutes that the perfusion was stopped the pressures and CO remained unchanged (Fig 3 *10 11 12*) After reperfusion insignificant hemodynamic changes occurred During and after perfusion the ischemic changes in the electrocardiogram remained constant Samples of tissue were obtained as before 30 minutes after the perfusion was stopped The lactic acid content of the nonischemic myocardium was 13 8 to 15 5 milligrams per cent that of the ischemic tissue was 20 6 to 21 2 and that of the perfused 6 9 to 9 6

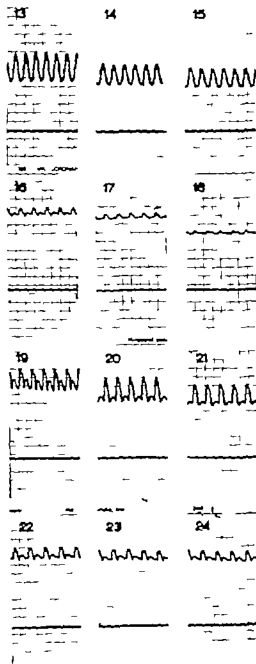


Fig 3 *13 16 19 22* Normal arterial pressure after the chest was opened *14 17 20 23* Pressure after coronary occlusion *15 18 21 24* After perfusion

B Perfusion of the posterior surface of the ischemic ventricular myocardium after occlusion of the circumflex coronary artery

In 25 mongrel dogs which weighed from 13 to 20 kilograms each anesthesia and ventilation were achieved as before and the circumflex coronary artery was occluded at its origin Thirty minutes after coronary occlusion perfusion of oxygenated or nonoxygenated Tyrode solution was made (1) into the middle of the cyanotic area of the posterior surface of the left ventricle in 5 dogs (2) into the boundary zone of the ischemic and nonischemic myocardium of the left ventricular border in 5 dogs (3) into the middle of the anterior surface of the left ventricle in 5 dogs and (4) into the posterior surface of the apex in the other 10 In each second dog the perfused Tyrode solution was bubbled with oxygen as before

The results of these perfusions are summarized in Table II and Fig 4

Table II Hemodynamic changes and cardiac output after perfusion of oxygenated or nonoxygenated Tyrode solution at normal atmospheric pressure into several regions of the ischemic left ventricular myocardium after occlusion of the circumflex coronary artery

Dog No.	Perfused region				Tyrode solution		Internal pressures (mm Hg)				LVEDP (cm H_2O)			CO (L/min)			Remarks
	Center cyanotic region	Boundary area	Noncyanotic region	Cyanotic apical region	Oxygenated	Nonoxygenated	Before coronary occlusion	After coronary occlusion	After perfusion	30 min after nonperfusion	Before coronary occlusion	After coronary occlusion	After perfusion	Before coronary occlusion	After coronary occlusion	After perfusion	
1	+				+		130/95	130/95	100/70	120/90	1.5	2.5	3.0	1.18	1.00	0.95	
2	+					+	130/100	100/70	80/60	90/60	1.0	2.0	3.0	1.50	1.30	1.00	
3	+				+		120/80	Fibrillation	60/40	40/20	2.0	3.0	3.0	1.10	0.40	0.35	Fibrillation recurred
4	+					+	140/100	100/60	60/40	70/50	0.5	2.0	2.5	1.40	1.20	1.10	
5	+				+		135/100	Fibrillation	50/30	—	1.5	6.0	6.5	1.05	0.40	0.30	Fibrillation recurred
6		+				+	150/110	110/90	80/70	90/70	3.0	4.0	4.5	1.00	0.90	0.80	
7		+			+		140/110	140/110	110/90	120/80	0.5	1.0	2.0	1.05	1.00	0.90	
8		+				+	170/80	90/70	70/50	80/50	1.5	3.0	3.5	1.20	1.00	0.90	
9		+			+		120/80	Fibrillation	60/40	60/40	2.0	6.0	6.5	1.20	0.50	0.45	
10		+				+	135/90	115/90	95/70	100/80	1.5	2.0	2.0	1.70	1.60	1.55	
11			+		+		110/80	90/70	80/70	80/70	3.0	4.5	5.0	1.10	1.00	0.80	
12			+			+	150/110	150/100	130/100	130/100	2.3	2.5	2.5	2.00	1.90	1.90	
13			+		+		130/100	110/100	90/70	90/?0	0.5	1.0	1.5	1.50	1.40	1.10	
14			+			+	125/85	125/90	105/70	115/80	0.8	1.0	1.0	1.60	1.60	1.50	
15			+		+		110/90	Fibrillation	55/30	55/30	4.0	6.0	2.0	1.10	0.40	—	
16			+	+		+	120/80	100/60	110/70	110/70	—	—	—	—	—	—	
17				+	+		135/105	95/70	115/80	115/80	1.5	2.0	2.0	1.70	1.50	1.60	
18				+		+	140/100	110/60	120/80	120/90	0.5	1.0	1.0	2.00	1.80	1.80	
19				+	+		110/80	Fibrillation	70/50	90/60	2.5	5.5	4.5	1.20	0.50	0.60	
20				+		+	130/110	130/110	130/110	130/110	0.5	0.5	0.5	1.50	1.40	1.40	
21				+	+		140/100	100/90	130/90	130/90	1.0	1.5	1.0	1.80	1.60	1.70	
22				+		+	160/110	130/100	150/100	150/100	1.5	2.0	2.0	1.90	1.60	1.?0	
23				+	+		110/70	90/60	100/70	100/70	0.5	1.5	1.5	2.10	2.00	2.00	
24				+		+	140/100	140/100	140/100	140/100	0.5	0.5	0.5	1.90	1.80	1.80	
25				+	+		120/90	Fibrillation	90/50	100/70	2.0	4.0	4.0	1.20	0.40	0.50	

Discussion

In our experiments the effects of the intramyocardial perfusions were dependent mainly on the area perfused. Perfusion into the center of the cyanotic region of the anterior or posterior ventricular surface, its boundary zone, or the neighboring non-ischemic myocardium had the effect of increasing the extrasystoles, decreasing the arterial pressures and CO, and increasing the LVEDP and venous pressures. When after about 30 minutes of coronary occlusion ventricular fibrillation failed to occur, it was induced with perfusion of myocardial regions other than the apex in one case after occlusion of the anterior descending coronary artery and in 2 after occlusion of the circumflex coronary artery. On the other hand, perfusion into the apex decreased the extrasystoles and increased the systemic pressures and CO if they had previously been decreased to different levels. These increased pressures and CO failed to reach the preocclusive levels. Perfusion into the apex was not complicated by ventricular fibrillation in any instance. No differences in the results were observed between oxygenated and nonoxygenated perfusion fluid. When after coronary occlusion and before perfusion ventricular fibrillation did occur and the heart was defibrillated, the arterial pressures and CO remaining at low levels, perfusion of any region of the myocardium increased the extrasystoles and LVEDP still more and further reduced the arterial pressure. Ventricular fibrillation reoccurred when the perfusion was continued for more than 15 to 22 minutes. This difference in the results, which was associated with the localization of the perfused area, was observed not only in the ischemic heart but also during perfusion of the normal heart. Several explanations can be advanced for these findings.

1. Effects of increased intramyocardial pressure after perfusion. It has been shown in hearts contracting in situ that a relationship exists between left ventricular systolic pressure and intramyocardial systolic pressure and that the pressures are correspondingly changed when cardiac performance is altered by epicardial compression.[11] We could not find information in the literature about the significance of increased intramyocardial pressure in hearts contracting isovolumetrically. In our experiments, intramyocardial perfusion into the ischemic apex increased the arterial pressures and CO and decreased the LVEDP and the extrasystoles. Quite different results were obtained after stiffening of the remaining ventricular regions of both the normal and the ischemic myocardium.

2. Anatomic and functional differences of the perfused myocardial area. Structurally, the apical portion of the left ventricle is composed entirely of the superficial bulbospiral muscle.[3] The function of this muscle is not expulsatory but is restricted to fixing the apical fulcrum and the atrioventricular valve leaflets. Expulsatory function falls mainly to the part of the deep cardiac muscles. That might explain why perfusion of the bulbospiral muscle failed to decrease the arterial pressures and CO of both the normal and ischemic ventricular myocardium. On the other hand, perfusion of the expulsatory muscles of the medioventricular anterior or posterior regions increased the extrasystoles and decreased the arterial pressures and CO. Ventricular fibrillation as a complication of perfusion of the myocardium occurred only when the expulsatory muscles were perfused. However, solely on the basis of the function of these muscles, these differences might account for perfusion of the normal but not of the ischemic myocardium. It is well known that the effectiveness of contractile power of the infarcted myocardial area is partly lost and that the expansion of this region during systole diminishes the cardiac output.[4] Resection of this infarcted area when located in the anterior left ventricular wall improves heart function and decreases mortality.[7] It is also known that after excision of a large segment of the anterior left ventricular wall and its replacement by a plastic graft[1] the possibility exists of the arterial pressures and cardiac output returning to the previous levels 2 to 3 hours after replacement.

3. Differences in collateral coronary blood flow in the perfused area. It is known that if the anterior descending coronary artery is tied close to its origin, fluorescein is injected into a femoral vein 1 minute later

the heart contractions are stopped by freezing and the heart is excised the filling of the ischemic area with yellow fluorescein will be incomplete The area which appeared to show less fluorescence as compared to the rest of the ischemic area was a region near the apex of the anterior wall of the left ventricle [11] After occlusion of the circumflex coronary artery no such area was found in the posterior wall of the apex However perfusion of the anterior or posterior wall of the ischemic apex after occlusion of the corresponding coronary artery increased the systolic arterial pressure and decreased the extrasystoles On the other hand perfusion of the remaining cyanotic areas or even of the neighboring nonischemic myocardium led to depressed heart action The latter may be attributed to the effect of a circumscribed increase in intramyocardial pressure during perfusion in these areas which decreased the local coronary circulation Increased intramyocardial pressure to the apex with less collateral circulation may result in occlusion of the capillaries of these areas and arrest capillary blood flow The anoxia of this nonexpulsatory area may be less important The obstruction of the coronary blood flow in the region of the apex due to the increased intramyocardial pressure may interfere with the collateral coronary blood flow and divert it to the neighboring ischemic region with expulsatory function thereby increasing its oxygenation and improving the heart action However when the perfusion was performed in an area with expulsatory function including not only the ischemic myocardium but also its boundary zone or neighboring nonischemic myocardium the coronary circulation was bound to be decreased a condition which is likely to affect its contractile strength This explanation being purely theoretical will be checked in some future experiments This we propose to do by adding radioactive substances to the perfused fluid and measuring the flow of blood in the perfused area and neighboring regions of the myocardium

4 Possible beneficial effect of washout of metabolites electrolytes and catecholamines from the perfused ischemic myocardium The constant finding that the lactic acid content of the tissue of the perfused ischemic area was much lower than that of the neighboring nonischemic area indicates that the perfused Tyrode solution was removing the metabolites from the perfused area This reduction in metabolites of the cyanotic region does provide an explanation for the selective beneficial results of the apical perfusions Reports in the literature indicate that an elevated concentration of potassium is found in the coronary venous blood after coronary artery occlusion [4] This higher level of potassium as compared to the content of potassium in the systemic veins and the low concentration of potassium in tissue during the first 24 hours after coronary artery occlusion indicates a considerable stagnation of the flow of blood in the veins of the ischemic myocardium [4] A relationship between ectopic activities and a high concentration of potassium in the coronary veins which drain the ischemic area has been described [3] In our laboratories determination by direct flame photometry of the levels of potassium in the magna cordis vein for 2 hours after occlusion of the anterior descending coronary artery did not show such an increased level of potassium Furthermore collection of the blood from the vena magna cordis for 2 hours after occlusion of the anterior descending coronary artery and reperfusion of this blood at a rate of 25 ml per minute into the circumflex coronary artery of 3 dogs (after previous release of the occluded anterior descending coronary artery) did not influence the heart action From these additional experiments we may conclude that the washout of potassium accumulated in the vessels of the ischemic region during myocardial perfusion cannot exert any fundamental influence on the results of myocardial perfusion

Analysis of the ischemic myocardial tissues adduces further evidence that prolonged ectopic activities must involve factors other than the shifts in electrolytes For example in the apex the concentration of catecholamines have been found to be higher than in the other regions of the left ventricle The infarct is known to lose about 75 per cent of its catecholamines within the 24 hours after coronary occlusion [12] The probability that the releas

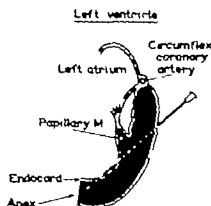


Fig 5 Erroneous insertion of the plastic needle into the ventricular cavity on its way to the apex

catecholamines by the ischemic myocardium is more marked at the apex may exert an influence on the decreased ectopic impulses after dilution of the released catecholamines by the Tyrode solution perfused into the apex Determination of catecholamines before and after perfusion will be performed in a series of future studies

Critical evaluation of the methods used

Dogs used for the purpose of our experiments weighed from 14 to 20 kilograms The average thickness of the left ventricular walls was 5 cm These animals are not ideal for studying intramyocardial perfusion If larger animals could be used the difficulties bound up with the exact insertion and fixation of the plastic perfusing needle would perhaps be less Thus when a needle is being inserted into the apex from the medioventricular region of the anterior left ventricular wall it may be inadvertently introduced into the ventricular cavity on its way to the apex (Fig 5) This faulty insertion of the needle happened several times in the course of our experiments and was discovered only after section of the heart because after the tip of the needle had entered into the muscular mass of the apex blood did not regurgitate through the lumen of the cannula Following a similar inadequate insertion the results of perfusion will naturally not be as expected The fixation of the plastic needle in the myocardium of the small hearts also constituted a problem The motion of the heart tends to expel the plastic needle This difficulty may be lessened when larger hearts are used or when preexisting cardiac hypertrophy is present

Summary

1 After occlusion of the anterior descending coronary artery perfusion of oxygenated or nonoxygenated Tyrode solution at a rate of 2 ml per minute into the center of the cyanotic region of the anterior surface of the left ventricle the boundary zone between cyanotic and noncyanotic regions or the noncyanotic neighboring myocardium resulted in a further decrease in the arterial pressures and cardiac output (CO) an increase in the left ventricular end diastolic pressure (LVEDP) and venous pressure and an increase in the extrasystoles Perfusion of the cyanotic apical region increased the arterial pressures and CO to below preocclusive levels and decreased the LVEDP and extrasystoles

2 After occlusion of the circumflex coronary artery perfusion of oxygenated or nonoxygenated Tyrode solution at a rate of 2 ml per minute into the center of the cyanotic region of the posterior left ventricular myocardium the boundary zone between the cyanotic and noncyanotic areas or the noncyanotic neighboring myocardium resulted in a further decrease in the arterial pressure and CO and an increase in the LVEDP venous pressures and extrasystoles Perfusion of the cyanotic apical region increased the arterial pressures and CO to below preocclusive levels and decreased the LVEDP and extrasystoles

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II Effects of intramyocardial perfusion of oxygenated Tyrode solution at 3 atmospheres absolute pressure into the ischemic left ventricular myocardium

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The increase in arterial pressure (AP) and cardiac output (CO) to below preocclusive levels during and after perfusion into the apex of the left ventricular myocardium after occlusion of one of its main coronary arteries[4] may be even higher if the perfused fluid contains a greater amount of dissolved oxygen, as for example after oxygenation at 3 atmospheres absolute (ATA). In order to evaluate these possibilities the following experiments were performed.

A. Perfusion of Tyrode solution oxygenated at 3 ATA into the ischemic left ventricular myocardium after occlusion of the anterior descending coronary artery

METHODS. Seventeen mongrel dogs which weighed from 14.2 to 17.3 kilograms each were used. Anesthesia was induced and maintained as previously described.[4] Ventilation was performed with 100 per cent oxygen. Pressures, CO, and ECG were recorded as before. While the anterior descending coronary artery was being prepared, the pressures in the high pressure chamber[1] were raised to 3 ATA. Thirty minutes after coronary occlusion, perfusion with oxygenated Tyrode solution at 3 ATA was performed in the cases in which the systolic arterial pressure and CO remained decreased and left ventricular end diastolic pressure (LVEDP) had increased. The Tyrode solution was bubbled 30 minutes before and during perfusion with oxygen through a porous aquarium stone at a rate of 2 liters per minute. The perfusion was performed by the previously described technique[4] into the center of the cyanotic region of the anterior left ventricular wall (Fig. 1) and into the anterior surface of the apex (Fig. 2).

RESULTS. After coronary occlusion the arterial pressures remained unchanged in 4 dogs and decreased in the others. The LVEDP increased and the CO decreased in all animals (Table I). The same ischemic ECG changes previously described occurred. After 5 to 30 minutes of oxygenation at 3 ATA the extrasystoles diminished significantly. In 5 dogs the ischemic ECG changes regressed, the arterial pressures and CO increased to about the preocclusive level, and the LVEDP decreased. Perfusions were performed in the other 8 dogs in which the pressures and CO remained below the preocclusive level. Perfusion in the center of the cyanotic region of the anterior surface of the left ventricle was then started in 4 dogs. During perfusion the extrasystoles increased and the arterial

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pressure and CO again decreased (Fig 3 I II III) whereas the LVEDP increased (Table I) During the next 2 hours of non perfusion the systemic pressures and CO increased and the LVEDP decreased again to the previous postocclusive levels

The ischemic ECG patterns diminished but did not disappear

Perfusion into the apex was performed in 4 dogs After 2 to 3 minutes of perfusion the arterial pressures and CO and the LVEDP returned to preocclusive levels

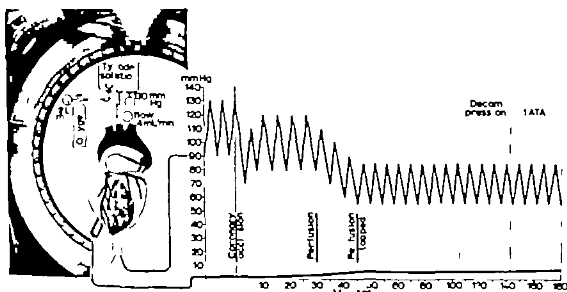


Fig 1 Hemodynamic changes after occlusion of the anterior descending coronary artery and perfusion of Tyrode solution oxygenated at 3 ATA into the center of the cyanotic region of the anterior surface of the left ventricle

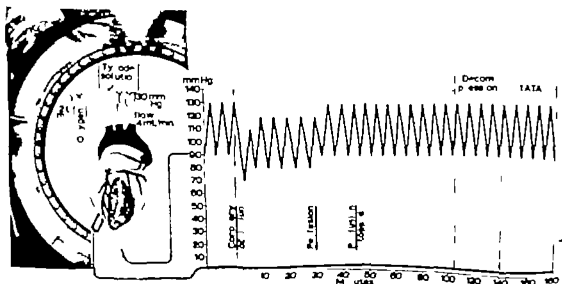


Fig 2 Hemodynamic changes after occlusion of the anterior descending coronary artery and perfusion of Tyrode solution oxygenated at 3 ATA into the cyanotic apical region

Table I. Hemodynamic changes and cardiac output after perfusion of Tyrode solution oxygenated of the anterior descending coronary artery

Dog No.	*Perfused region*		*Perfusion not performed*	*Arterial (mm*	
	Center cyanotic region	*Cyanotic apical region*		*Before coronary occlusion*	*After coronary occlusion*
1	+			120/80	100/80
2			+	120/90	170/90
3			+	110/80	110/80
4			+	130/110	130/110
5	+			140/110	120/110
6	+			135/90	115/70
7			+	160/120	160/120
8	+			130/90	110/80
9		+		120/80	100/60
10			+	120/80	120/80
11		+		140/110	110/90
12			+	160/120	160/120
13			+	170/120	170/120
14		+		150/120	125/100
15			+	120/80	120/80
16			+	130/100	130/100
17		+		130/100	100/80

Table II. Hemodynamic changes and cardiac output after perfusion of Tyrode solution oxygenated of the circumflex coronary artery

Dog No.	*Perfused region*		*Perfusion not performed*	*Arterial (mm*	
	Center cyanotic region	*Cyanotic apical region*		*Before coronary occlusion*	*After coronary occlusion*
1	+			120/80	100/70
2	+			110/60	Fibr
3			+	140/90	140/90
4	+			130/100	100/80
5			+	160/110	160/110
6	+			110/80	100/70
7			+	145/120	145/120
8		+		120/70	Fibr
9			+	160/110	160/110
10		+		140/100	100/90
11			+	145/110	145/110
12			+	135/100	135/100
13		+		150/100	110/60
14		+		160/100	120/90
15			+	150/110	150/110
16			+	120/80	120/80
17		+		120/80	90/70
18			+	150/100	150/100
19			+	130/90	130/90
20			+	140/100	140/100

at 3 ATA into several regions of the ischemic anterior left ventricular myocardium after occlusion

pressures Hg)		LVEDP (cm H_2O)			CO (L/min)		
After perfusion	*30 min after nonperfusion*	*Before coronary occlusion*	*After coronary occlusion*	*After perfusion*	*Before coronary occlusion*	*After coronary occlusion*	*After perfusion*
80/60	100/80	2 0	3 5	5 0	2 00	1 0	1 40
—	—	2 0	2 5	—	1 50	1 40	—
—	—	2 5	3 0	—	1 90	1 90	—
—	—	1 5	2 0	—	1 70	1 10	—
90/70	170/100	0 0	2 0	3 5	—	—	—
85/60	115/60	1 0	1 5	3 0	00	1 60	1 40
—	—	0 0	0 5	—	2 00	1 80	1 50
85/60	110/60	2 0	3 0	—	1 60	1 70	—
120/80	120/80	3 0	3 5	—	1 0	1 60	—
—	—	0 0	1 0	—	1 40	1 40	—
140/90	140/100	1 0	2 5	2 5	2 00	1 80	2 0
—	—	2 0	2 5	—	1 40	1 30	1 35
—	—	1 0	2 5	—	—	—	—
150/120	150/120	1 5	1 5	—	—	—	—
—	—	1 5	2 0	—	1 60	1 50	—
—	—	1 5	2 5	—	1 50	1 40	—
130/100	130/100	2 0	2 5	1 5	1 40	1 30	1 40

at 3 ATA into several regions of the ischemic posterior ventricular myocardium after occlusion

pressures Hg)		LVEDP (cm H_2O)			CO (L/min)		
After perfusion	*30 min after nonperfusion*	*Before coronary occlusion*	*After coronary occlusion*	*After perfusion*	*Before coronary occlusion*	*After coronary occlusion*	*After perfusion*
80/ 0	100/ 0	3 0	4 0	5 5	1 40	1 10	1 00
Fibr	60/40	1 5	4 0	5 0	1 60	1 00	0 60
—	—	1 5	2 0	—	2 00	1 90	—
60/40	100/60	2 0	4 0	4 5	1 10	1 00	0 8
—	—	1 5	1 8	—	2 00	1 85	—
70/50	100/ 0	2 5	4 0	—	1 60	1 40	—
—	—	3 0	3 5	—	1 60	1 50	—
100/70	120/70	1 5	2 5	—	1 30	—	—
—	—	2 0	2 5	—	1 90	1 80	—
140/100	140/100	3 0	4 0	4 5	00	1 0	1 85
—	—	1 0	1 5	—	1 70	1 00	—
—	—	0 0	0 5	—	1 10	1 00	—
150/100	150/100	0 5	1 5	1 0	1 90	1 60	1 0
160/100	160/100	3 0	4 0	4 0	1 60	1 30	1 5
—	—	2 0	2 5	—	1 50	1 40	—
—	—	1 5	1 5	—	1 40	1 20	—
120/80	170 80	0 2	3 5	2 5	1 30	1 10	1 20
—	—	2 0	2 5	—	1 20	1 10	—
—	—	3 0	3 0	—	1 25	1 10	—
—	—	2 0	3 0	—	1 35	1 20	—

(Fig. 3 IV V VI) The ECG remained unchanged. After 15 minutes of perfusion and during the next 60 minutes of nonperfusion the pressures remained unchanged and the ischemic ECG changes regressed. In the nonperfused animals the pressures also remained stable at preocclusive levels and the ECG changes also regressed. During and 1 hour after decompression the ischemic ECG changes reappeared in all animals. However, the systolic arterial pressure remained unchanged, the venous and LVEDP pressure increased slightly, and the CO decreased.

B. Perfusion of Tyrode solution oxygenated at 3 ATA into the ischemic left ventricular myocardium after occlusion of the circumflex coronary artery.

Twenty dogs which weighed between 14.6 and 18.5 kilograms were used. The circumflex coronary artery was prepared. After the pressure had been raised to 3 ATA, the circumflex coronary artery was tied as near as possible to its origin. Thirty minutes after occlusion in the animals in which the arterial pressure was decreased, perfusion was performed in the following two regions: (a) the center of the cyanotic area of the posterior left ventricular wall and (b) the posterior surface of the apex.

RESULTS. Some minutes after coronary occlusion during oxygenation at 3 ATA ventricular fibrillation occurred in 2 dogs. The institution of heart massage and defibrillation easily restored the heartbeat. Five minutes after coronary occlusion the pressures and CO remained unchanged in 11 dogs, the CO being slightly decreased. In the other 9 the arterial pressures decreased and the LVEDP increased. Ischemic ECG changes occurred during the first 5 minutes after coronary occlusion. The dogs in which the arterial pressure was not decreased were not perfused. Perfusion was performed into the center of the cyanotic region of the posterior surface of the left ventricular myocardium in 4 dogs. During perfusion ventricular fibrillation occurred in one of them. However, defibrillation was possible, with the arterial pressures and CO remaining at low levels. In the other dogs the extrasystoles increased still more, the CO and arterial pressures decreased (Fig. 3 VII, VIII, IX), and the LVEDP increased (Table II). After the perfusion was stopped and during 2 hours of hyperbaric oxygenation the arterial pressures and CO increased but remained at a level lower than the preocclusive pressures. The ischemic ECG changes persisted.

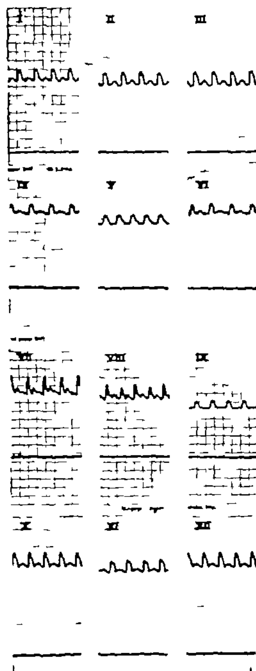


Fig. 3. I, IV, VII, X. Normal arterial pressure after the chest was opened. II, V, VIII, XI. Pressures after coronary occlusion. III, VI, IX, XII. After perfusion.

Perfusion was performed into the posterior apex of the left ventricle in 5 dogs with decreased postocclusive arterial pressure and CO and increased LVEDP. Within 2 to 15 minutes after perfusion the CO and arterial pressures returned to about the preocclusive level in all dogs (Fig 3 X, XI, XII). In the nonperfused group of dogs the arterial pressures remained unchanged and the ECG changes regressed. During the next 2 hours of hyperbaric oxygenation the ischemic ECG picture regressed (Table II). During 1 hour after decompression the pressures showed only insignificant changes and the CO decreased slightly.

C Comparison of the effects of perfusion of the ischemic myocardium with Tyrode solution oxygenated at 1 and 3 ATA in the same animals

In 5 mongrel dogs which weighed between 14.3 and 18 kilograms and which were anesthetized and ventilated as described previously, the anterior descending coronary artery was occluded 1 cm below its origin. Thirty minutes later when the arterial pressures and CO had decreased and the LVEDP had increased, oxygenated Tyrode solution at 1 ATA was perfused into the anterior surface of the apex by the same technique for 15 minutes. The intramyocardially inserted plastic needle was then fixed into place with some drops of Eastman 910 adhesive.[3] After 2 hours the atmospheric pressure was raised to 3 ATA. Thirty minutes later when the pressures remained constant at the previous level, the apex was perfused for 15 minutes with oxygenated Tyrode solution at 3 ATA.

RESULTS. After coronary occlusion the arterial pressures and CO decreased in 4 animals. In the fifth animal ventricular fibrillation occurred 5 minutes after occlusion. This animal was replaced by another in which the systemic pressures after coronary occlusion also decreased to about the same level. After 30 minutes of occlusion perfusion of the apex was started. During the 15 minutes of perfusion the arterial pressures and CO of all animals increased and the LVEDP decreased. During the following 60 minutes the pressures remained unchanged. After 10 minutes of hyperbaric oxygenation the systemic arterial pressures, the LVEDP, and the CO returned to about the preocclusive levels in 2 dogs and the ischemic ECG patterns disappeared. In the other 3 animals the arterial pressures and CO were still lower than the initial preocclusive levels. Six to 8 minutes after perfusion at 3 ATA the CO and arterial pressures returned to the preocclusive levels (Fig 4 XIII, XII, XI, XVI, XVII). The ischemic ECG changes regressed. During the next 60 minutes of hyperbaric oxygenation the arterial pressures and CO remained unchanged. During and after decompression the ischemic ECG pictures reappeared, the arterial pressures remaining unchanged during the 1 hour of observation time. The CO decreased slightly (Table III).

Control experiments. These experiments were necessary in order to compare the foregoing results with those of simple coronary occlusion during oxygenation at 3 ATA. Twenty five dogs which weighed between 12.2 and 16.5 kilograms were used

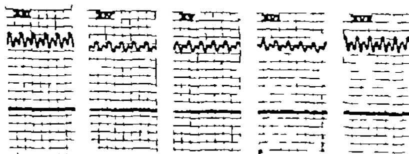


Fig 4 XIII Normal arterial pressure after the chest was opened. XII Pressures after coronary occlusion. XI After perfusion. XVI After hyperbaric oxygenation. XVII After perfusion at hyperbaric oxygenation.

Table III. Comparison of the hemodynamic changes and cardiac output after perfusion of the apex of the ischemic left ventricular myocardium after occlusion of the anterior descending coronary artery with Tyrode solution oxygenated at 1 ATA and 3 ATA in the same animals

Dog No.		Before coronary occlusion	After 30 min coronary occlusion	After 15 min perfusion at 1 ATA	After oxygenation at 3 ATA	After 15 min perfusion at 3 ATA	After 2 hr non perfusion at 3 ATA	After decompression
1	Arterial pressure (mm Hg)	120/80	100/60	110/70	110/70	120/80	120/80	120/80
	LVEDP (cm H_2O)	2.00	4.00	3.00	3.00	2.50	2.50	2.80
	CO (L/min)	1.90	1.60	1.70	1.75	1.80	1.85	1.90
2	Arterial pressure (mm Hg)	160/110	130/90	145/100	145/100	160/110	160/110	160/110
	LVEDP (cm H_2O)	0.50	2.00	1.50	1.50	1.00	1.00	1.20
	CO (L/min)	1.40	1.20	1.25	1.30	1.35	1.35	1.30
3	Arterial pressure (mm Hg)	150/110	125/90	135/100	135/100	150/110	150/110	130/110
	LVEDP (cm H_2O)	1.00	2.50	2.00	2.00	1.50	1.50	1.70
	CO (L/min)	1.80	1.60	1.60	1.70	1.75	1.75	1.70
4	Arterial pressure (mm Hg)	130/90	110/70	120/80	120/80	130/90	130/90	130/90
	LVEDP (cm H_2O)	2.50	4.00	3.50	3.50	3.00	3.00	3.00
	CO (L/min)	1.60	1.30	1.40	1.40	1.50	1.50	1.40
5	Arterial pressure (mm Hg)	145/120	115/100	130/110	130/110	145/110	145/110	145/110
	LVEDP (cm H_2O)	2.50	3.50	3.00	3.00	2.50	2.50	2.70
	CO (L/min)	2.00	1.70	1.70	1.85	1.90	1.95	1.85

When the pressure of 3 ATA was reached the circumflex coronary artery was occluded as before. After 2 hours of ventilation at 3 ATA the surviving animals were decompressed and ventilated with 50 per cent oxygen and room air for 1 hour and then sacrificed.[7]

RESULTS. Two to 10 minutes after occlusion of the coronary artery ventricular fibrillation occurred in 5 animals. Defibrillation was successful but irreversible ventricular fibrillation recurred in 2 of them. The arterial pressure and CO in the other 20 dogs decreased in 7 and remained unchanged in 13. The LVEDP increased. When decreased the arterial pressures returned to the preocclusive level within 10 to 28 minutes in 5 animals and remained unchanged in 2 during the 2 hours of hyperbaric oxygenation. The LVEDP decreased. During and 1 hour after decompression the arterial pressures remained unchanged in 19 dogs and decreased slightly in the other 4. The LVEDP and venous pressure increased slightly.

Discussion

The effect of the increased oxygen carrying capacity of the intramyocardially perfused fluid on the function of the ischemic myocardium could be best evaluated during perfusion of Tyrode solution oxygenated at 3 ATA. Perfusion of oxygenated or nonoxygenated Tyrode solution at normal atmospheric pressure into the ischemic region of the apex resulted in in

creased arterial and CO pressures to under the preocclusive levels.[4] The ECG continued to show ischemic patterns. On the other hand, perfusion of the same area with Tyrode solution that contained *larger amounts of dissolved oxygen* (about 6.9 volumes per cent) during oxygenation at 3 ATA[2] tended to increase the pressures to the preocclusive levels and decrease the extrasystoles. The ischemic changes shown by the ECG were reversed, although ischemia of the perfused region persisted and even increased. A question that is as yet unanswered during hyperbaric oxygenation is the extent to which the ischemic tissues can derive oxygen by diffusion from a neighboring area that has a normal supply of blood. The supply of oxygen to the metabolizing cells can be interfered with not only by an inadequate supply of blood but also by any other factor that interferes with the diffusion from the capillaries to the cells.[3] Edema fluid is an example of such a barrier. It is well known that the water content of the infarct is increased within 1 hour after coronary occlusion.[8] Extensive myocardial edema has also been found several times in cases of sudden death associated with atheromatous coronary vessels, even when no thrombosis of these vessels was present.[4] Although polarographic studies of the oxygen tension of the ischemic myocardium during hyperbaric oxygenation are still lacking in the literature, it is evident that the decreased flow of blood into the ischemic area may prevent adequate oxygenation of the stagnated tissue fluid to a level approximating that of the perfused Tyrode solution.

In the last series of comparative experiments the influence of the oxygen carrying capacity of the perfused fluid was more clearly demonstrated. By perfusion of oxygenated Tyrode solution at 1 ATA into the ischemic apex of the left ventricle the pressures were increased, although they did not reach the preocclusive level. When these perfusions were repeated, this time at 3 ATA, in the same animals, the arterial pressures increased to preocclusive levels. However, we cannot exclude the possibility that an indirect beneficial effect of the increased dissolved oxygen on the collateral coronary blood flow in the remaining nonperfused myocardial area during oxygenation at 3 ATA might have yielded similar results. In our control experiments, occlusion of a major coronary artery, such as the circumflex coronary artery, during hyperbaric oxygenation caused the arterial pressure and CO, when decreased, to return to the preocclusive level within 10 to 28 minutes. Only in 16 per cent of the cases did the pressures remain decreased during 2 hours of hyperbaric oxygenation.[7] On the other hand, when the ischemic apical region was perfused, the pressures returned to the previous levels within 2 to 4 minutes after the perfusion had started. Allowing for the results in the control dogs, we think that it is necessary to make a certain reservation in comparing the results of direct perfusion of oxygenated fluids with the results of simple oxygenation at 3 ATA. A large number of experiments will be required in order to come to a more accurate evaluation of these questions. The beneficial effect of myocardial perfusion at 3 ATA may also be attributed to the fact that the perfused oxygenated fluid not only restored the tissue fluid minute volume mechanically, i.e., by washing out the stagnating tissue fluid in the ischemic area which contained a large amount of metabolites, but also exerted a direct influence on the myofibrils immersed in the oxygenated fluid, thereby restoring the inadequate oxygenation. Myographical studies of the contractility of the perfused region as well as polarographic studies of its oxygen tension differences during perfusion were not performed because these studies will be the purpose of future investigations. More difficult is an explanation of why the perfusion of the same oxygenated fluid at 3 ATA in the middle of the cyanotic area of the anterior or posterior ischemic regions of the left ventricle yielded such deviant results. Whether any difference does exist in the rate of diffusion of the perfused fluid into these regions and into the apex is a question which should equally be investigated with radio-labeled fluids. From the foregoing we may conclude that, although hyperbaric oxygenation improves heart function after coronary occlusion, additional intramyocardial perfusion of the anoxic apex with oxygenated Tyrode solution at 3 ATA may be considered in cases in which

there is failure of restoration of ECG findings and arterial pressures after simple hyperbaric oxygenation

Summary

1 After occlusion of the anterior descending coronary artery during hyperbaric oxygenation at 3 ATA and in the presence of decreased arterial pressure and cardiac output (CO) perfusion of oxygenated Tyrode solution at a rate of 2 ml per minute into the center of the cyanotic region of the anterior surface of the left ventricle resulted in a further decrease in the pressures and CO and an increase in the left ventricular end-diastolic pressure (LVEDP) and extrasystoles Under the same conditions perfusion of the ischemic apical area resulted in an increase in arterial pressures and CO to the preocclusive levels The pressures and CO were maintained at about the same level in the course of 2 hours of hyperbaric oxygenation and 1 hour after decompression

2 After occlusion of the circumflex coronary artery during hyperbaric oxygenation at 3 ATA and in the presence of decreased arterial pressures and CO perfusion of oxygenated Tyrode solution at a rate of 2 ml per minute into the center of the cyanotic region of the posterior left ventricular myocardium decreased the arterial pressure and CO still more and increased the LVEDP and venous pressures Ventricular fibrillation occurred in one animal Under the same conditions perfusion into the ischemic apical area resulted in an increase in arterial pressures and CO to preocclusive levels within 2 to 5 minutes The pressures remained stable in the course of 2 hours of hyperbaric oxygenation and 1 hour after decompression

3 After occlusion of the anterior descending coronary artery and in the presence of decreased arterial pressure and CO perfusion of Tyrode solution at a rate of 2 ml per minute oxygenated at normal atmospheric pressures into the cyanotic apical region increased the arterial pressures and CO to levels lower than those before occlusion When the perfusions were repeated 1 hour later with oxygenated Tyrode solution at 3 ATA the pressures and CO reached the preocclusive level within 6 to 8 minutes The pressures remained unchanged in the course of 2 hours of hyperbaric oxygenation and 1 hour after decompression

4 After occlusion of the circumflex coronary artery during oxygenation at 3 ATA the arterial pressures when decreased increased to preocclusive levels *within 30 minutes* of hyperbaric oxygenation in 84 per cent of the animals and remained unchanged in the course of 2 hours of hyperbaric oxygenation in 16 per cent The increased LVEDP and venous pressure decreased slightly

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A measuring probe to facilitate measurement of cardiovascular structures displayed on radiographs

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Increasing interest in the accurate measurement of cardiovascular structures has grown with the rapid expansion of cardiac catheterization and angiographic techniques. Rapid film changers and motion picture equipment have permitted correction of diameter changes during cardiac cycle phases. Biplane techniques using lead markers or rings as phantoms have enabled some workers to make necessary distortion corrections.[1-4] Orthodiagraphy and teleorentgenography, older techniques, are limited to the study of static images and are not suitable for use with angiography.[5] A technique used to get around the problem of absolute measurement is the ratio of one part to another.[6] Another solution supported by Braunwald and others[7,8] is the calculation of the volume of the aortic segments from pressure volume tables of the aortas of cadavers prepared by Remington and associates. In the field of x-ray pelvimetry, Thoms and Wilson[9] incorporated a radiopaque marker in the same



Fig. 1. *Left*, Radiograph of measuring guide showing alternating radiopaque and radiolucent elements. *Right*, Photograph of measuring guide with centimeter ruler.

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plane as the part of the pelvis they were measuring.[illegible] A reasonable solution, especially for work in a single plane, was described by Moncada and associates[10] when they measured the size of ventricular septal defects revealed by left ventricular angiography by comparing them to the known diameter of the cardiac catheter used for injection purposes. The disadvantages of this technique would seem to lie in the crucial measurement of the small round catheter diameter. Wood,[11] in an unreported study, used ring-marked catheters in a similar way.

At my request the United States Catheter and Instrument Corporation, Glens Falls, New York, constructed a 140 cm. probe with a diameter of 0.039 inches and alternating 1.0 cm. radiolucent and radiopaque segments in the distal 30.0 cm. (Fig. 1). This probe is coated with plastic material and may be easily passed directly into a vessel or by needle (17 gauge) or catheter (No. 8 French) to the part of the cardiovascular system under study. Using a simple proportionality, all structures in the same plane as the probe may be easily and exactly measured. Because of its small diameter, flexibility, and considerable length, it would presumably be useful in problems of radiographic measuring outside the cardiovascular system.

Summary

A measuring probe for aid in precise radiographic measurements in the cardiovascular system has been described along with a brief review of other measuring methods.

Dr. Samuel Landau and Mr. Leonard Kaplan provided technical assistance.

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Case report

Right ventricular aneurysm, a complication of transventricular pulmonary valvulotomy

Report of two cases, one associated with gonadal agenesis

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This report is concerned with the development of a cardiac aneurysm at the site of a right ventriculotomy performed for the relief of valvular pulmonary stenosis.

Case reports

Case 1 (*J.H.H. 974 22 87*). F. E. was a 12 year old white boy in whom a heart murmur had first been detected when he was 9 months old. Dyspnea and cyanosis were noted when he was 5 years old. When he was 6 years old, the diagnosis of pulmonary stenosis was made, and 3 years later, in November, 1953, he underwent a transventricular pulmonary valvulotomy at another hospital. One month after operation the patient developed a febrile illness which was diagnosed and treated as subacute bacterial endocarditis, even though no positive cultures of blood were obtained. In the following months the size of his heart was noted to increase progressively, and his exercise tolerance, which had improved after the operation, again markedly decreased. In June, 1956, he was referred to the Harriet Lane Home Cardiac Clinic for evaluation.

On *physical examination* he appeared to be fairly well developed and well nourished, with no cyanosis. His height was 135.75 cm. and his weight was 29.71 kilograms. The blood pressure was 90/75 mm. Hg. The chest was asymmetrical, with a marked precordial prominence. The precordium was active, and a systolic lift was both visible and palpable along the left midsternal border; the lift was associated with a slight intercostal retraction at the apex. The apex beat was in the fifth left intercostal space 2 cm. beyond the midclavicular line. A harsh systolic murmur, Grade 3 in intensity on the basis of Grade 6 as maximal intensity, accompanied by a faint thrill, was present in the third left intercostal space. A short early diastolic murmur was heard in the same area. A high-pitched musical systolic murmur was present at the apex. The pulmonary second sound was absent. The liver was felt 3 cm. below the right costal margin and pulsated with each systole. The remainder of the physical examination was not remarkable.

Laboratory data revealed a hemoglobin of 15.1 Gm. per cubic milliliter and a hematocrit of 51 per cent.

Fluoroscopy showed marked cardiac enlargement. In the anteroposterior view the right atrium appeared to be prominent. The pulmonary artery segment was large. In the right anterior oblique view the right ventricle was enlarged. In the lateral projection there was a pulsating mass in the area of the right ventricular outflow tract. The pulmonary vascularity was decreased. X-ray examination confirmed the fluoroscopic findings.

The electrocardiogram showed first degree atrioventricular block with marked right atrial and right ventricular hypertrophy.

Cardiac catheterization revealed a right ventricular systolic pressure of a 199 mm. Hg and end-diastolic pressure of 14 mm. Hg. The systolic pressure in the left pulmonary artery was 15 mm.

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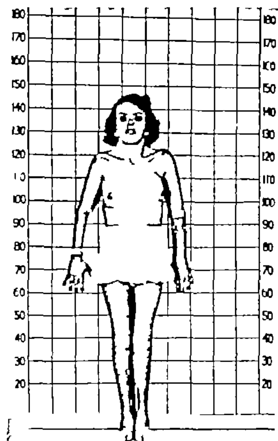


Fig 1 Case 2 (B I #55 07 66) Note the bilateral ptosis hypertelorism short webbed neck well developed breasts and the precordial bulge caused by the aneurysm

Hg and the diastolic pressure was 7 mm. Hg The *pull back tracing from the pulmonary artery sug*gested the presence of an nfundibular chamber The peripheral arterial saturation was 95 per cent

Operation was performed by Dr Henry Bahnson on Aug 11 1956 w th the u e of cardiopulmonary bypass A saccular aneury m arose from the out flow tract of the right ventricle t the site of the previous ventriculotomy Tiny atheromatous plaques were felt in the wall of the aneury m The section of the aneurysmal sac showed hyaline scars and calcification The pulmonary alve was nar rowed The right anterior commu sure had been opened presumably during the previou operation The aneurysm was resected and the pulmonary valve dilated

Although the patient returned to the recovery room in satisfactory condition he developed hyper pyrexia and circulatory collapse and died on the fifth postoperative day

Autopsy (#26671 performed by Dr T Williams) showed that the heart was greatly enlarged with marked hypertrophy of the right entricle and dilatation of the right atrium The pulmonary valve was found to be stenotic The right ven tricular aneurysm had been sati factorily resected The lungs showed hemorrhage and atelectasis and the kidneys showed tubular necrosis and casts

Case 2 (B I #55 07 66) B I a wh te girl was *first seen in the Harriet Lane Home Cardiac Clinic* in 1950 when she was 11 years old Cyanosis and a heart murmur were noted at birth The patient had an unusual facies and was mentally retarded Her growth was stunted and her development was markedly delayed She showed moderate dyspnea on exertion and easy fatigability X ray films re ealed moderate cardiac enlargement with a con cavity in the area of the pulmonary conus Cath eterization of the right side of the heart demon strated an atrial septal defect and a right ventricu lar pressure of 126 mm Hg the pulmonary artery was not entered The peripheral arterial saturation was 73 per cent A diagnosis of pulmonary stenosis with intact ventricular septum and an associated atrial septal defect was made In September 1950 the patient underwent a transventricular pulmonary alvulotomy by Dr Alfred Blalock At operation the pulmonary artery was found to be large with aneurysmal dilatation of the sinuses of Valsalva There were also many aneurysmal like nodules surrounding the main pulmonary artery The pul

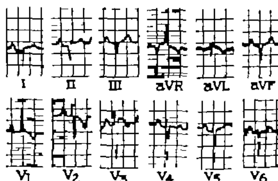


Fig 2 Ca e 2 Electrocardiogram



Fig 3 Case 2 Anteroposterior x ray film shows aneurysm of the right ventricle

monary valve was stenotic and partially calcified The postoperative course was complicated by intrathoracic bleeding The general condition of the patient improved slightly after surgical treatment. A postoperative catheterization of the right side of the heart showed a right ventricular pressure of 97/34 mm Hg The pulmonary artery was not entered Three months postoperatively a bulge was first noted over the precordium Fluoroscopy revealed a pulsatile mass in the area of the outflow tract of the right ventricle which expanded with systole The diagnosis of right ventricular aneurysm was made Angiocardiography performed in February 1951 demonstrated an atrial septal defect and residual pulmonary stenosis

The patient refused further surgery and did not return to the clinic until 1961 She was then 22 years of age and was leading a moderately restricted life in a home for handicapped children Her main complaint was a progressively increasing bulge over the left precordium

On physical examination she was short and underdeveloped with bilateral ptosis hypertelorism webbing of the neck and slight bilateral exophthalmos (Fig 1) There were bilateral simian lines in the palms of the hand and extremely wide carrying angles at the elbow The breasts were well developed There was cyanosis and clubbing of the extremities There was a slight pectus excavatum The precordium was very active Between the apex and the mid left sternal border there was a protruding mass 14 by 14 cm which pulsated with each systole (see Fig 1) A faint systolic thrill was palpable over the mass In addition a systolic thrill was present in the second left intercostal space close to the sternal border over the same area a harsh ejection type of systolic murmur (Grade 4 murmur on the basis of Grade 6 as maximum intensity) was heard The pulmonary second sound was absent The blood pressure was 125/80 mm Hg

Laboratory data revealed a hemoglobin of 21 6 Gm per cubic milliliter and a hematocrit of 70 5 per cent Chromosomal studies were attempted but the extreme polycythemia prevented satisfactory culture so that no results were obtained

The electrocardiogram showed right atrial and marked right ventricular hypertrophy (Fig 2)

The x ray examination showed marked cardiac enlargement with aneurysmal dilatation of the area of the right ventricular outflow tract (Fig 3) The pulmonary vascularity was normal There was calcification in the area of the main pulmonary artery On fluoroscopy the aneurysmal mass expanded with ventricular systole and appeared to be continuous with the right ventricle The venous angiocardiogram was compatible with the diagnosis of right ventricular aneurysm

Operation was performed by Dr David Sabiston on Oct 3 1961 using cardiopulmonary bypass The aneurysm which arose from the outflow tract of the right ventricle at the site of the previous ventriculotomy had eroded the anterior chest wall and had ruptured into the subcutaneous tissue In spite of this the aneurysm was successfully excised The pulmonary valve was found to be completely calcified The pulmonary stenosis was relieved by the excision of two leaflets and the insertion of a Teflon patch in the outflow tract The right atrium was opened and a 3 cm atrial septal defect was closed The postoperative course was complicated by severe respiratory distress which necessitated tracheotomy The patient died in circulatory collapse on the second postoperative day

Autopsy (#31023 performed by Dr B A Herrero) showed that the heart was moderately enlarged with marked right atrial dilatation and right ventricular hypertrophy The pulmonary valve was thickened and calcified The right ventricular aneurysm had been satisfactorily repaired The lungs were edematous and the tracheobronchial tree was filled with bloody material Microscopic studies showed hyaline membrane formation lining the alveoli of the lungs The ovaries were elongated the capsules were smooth and no normal architectural pattern was present On section the ovaries had a rather whitish gray appearance Histologic examination of the ovaries showed only sparse stromal cell population no follicles were seen The uterus measured 6 5 cm in length microscopic examination showed almost complete absence of the endometrium

Anatomic diagnosis Surgical resection of right ventricular aneurysm and closure of atrial septal defect postoperative hemorrhage in the pleuropericardial cavity pulmonary congestion and edema Gonadal agenesis

Discussion

Myocardial aneurysm is very unusual in childhood and adolescence Zeeman and associates[1] recently reported a case of left ventricular aneurysm which occurred in a 16 year old boy with granulomatous myocarditis and they reviewed the etiology of the few cardiac aneurysms which have been seen in childhood and adolescence The etiology was varied and included congenital defects of the myocardium myocardial infarction secondary to an anomalous left coronary artery from the pulmonary artery rheumatic myocardial necrosis and Chagas disease Trauma also has been reported to be an etiological agent

In our two cases the ventricular aneurysm was almost certainly related to previous cardiac surgery Both patients had undergone a transventricular valvulotomy and in both the aneurysm arose from the right ventricular outflow tract at the site of the ventriculotomy In both instances the aneurysm caused a visible and palpable precordial bulge which could be seen upon fluoroscopy and was visualized by angiocardiogram

Aneurysms of this origin are fortunately rare To the best of our knowledge the only other case of right ventricular aneu

rysm which developed after transventricular valvulotomy for pulmonary stenosis with intact ventricular septum was that reported by Derra and Loogen. A similar complication, however, has been observed in a few patients after pulmonary valvulotomy or infundibular resection for tetralogy of Fallot.[3,4] Recently, Stansel and associates[6] reported a case of right ventricular aneurysm secondary to a bullet injury which was successfully repaired with the aid of temporary cardiopulmonary bypass. Postoperative left ventricular aneurysms have also been reported to have occurred after surgical correction of aortic and mitral valve disease.[7,8]

The pathogenesis of postoperative ventricular aneurysm is not yet established with certainty; probably several factors acting separately or in conjunction play a role. Kerr and associates[7] in their comprehensive study of left ventricular aneurysms discussed in detail the role of infection, faults in surgical technique, and residual high ventricular pressure. These authors suggested that, as in the case of aneurysms associated with coronary artery disease, myocardial infarction may be a factor. They postulated that in damaged hearts interstitial hemorrhage and edema after instrumentation may devitalize surrounding muscle fibers and produce a small area of infarction in the heart wall.

One of our two patients (Case 1) did have an unexplained infection, possibly a subacute bacterial endocarditis 1 month after operation. The second patient had a most unusual type of pulmonary stenosis, in that the valve was found to contain calcium when she was 11 years of age and was severely calcified when she was 22 years old. In these two cases the pulmonary stenosis either was not completely relieved or had recurred. The persistence or recurrence of the pulmonary stenosis is undoubtedly an important factor, but that alone can hardly be the cause, since a number of cases have been reported in which the pulmonary stenosis was either not relieved or recurred but in which no aneurysm of the right ventricle developed.[10]

It is also noteworthy that the second patient (B. I.), in addition to pulmonary stenosis, had ovarian agenesis (Turner's syndrome). Gonadal agenesis is well known to be associated with congenital malformations of the cardiovascular system. Raimer, Pope, and associates[11] reported 39 cases of Turner's syndrome, in 16 of which there were cardiovascular malformations. Among these were 7 patients with coarctation of the aorta, and 7 who had pulmonary stenosis. Of the other 2 patients, one had total anomalous pulmonary venous return and the other had an atrioventriculare communue type of defect.

It is known that patients with ovarian agenesis tend to form keloid at the site of skin incision.[12] Whether this tendency to the formation of keloid is in any way related to the development of a right ventricular aneurysm is unknown.

Summary

Two cases of right ventricular aneurysm which developed in young patients after transventricular valvulotomy for pulmonary stenosis with intact ventricular septum are presented. The pathogenesis of this unusual complication appears to be related in part to the incomplete relief of the pulmonary stenosis and the consequent residual high right ventricular pressure. That such is not the sole cause is indicated by the rarity of such aneurysms in patients who require reoperation for pulmonary stenosis. Infection may have also been a factor in the first patient, since he was suspected of having had subacute bacterial endocarditis. The second patient had ovarian agenesis, as well as an unusual calcification of the pulmonary valve even at the time of the first operation. The relationship of these factors to the formation of the aneurysm is unknown.

A diagnosis of aneurysm of the right ventricle was suspected on the basis of a visible and palpable precordial bulge and was confirmed by fluoroscopy and angiocardiography.

Although both patients died after surgical treatment entailing excision of the aneurysm and relief of the pulmonary stenosis, surgical correction appears to be the only possible treatment.

We are most grateful to Dr. Helen B. Taussig for her advice and help in the preparation of this manuscript. We wish also to express our appreciation to Dr. H. W. Jones, Jr., and Dr. R. H. Heller for the review of the histologic sections from the patient with gonadal agenesis.

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Clinical pathologic conference

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This 20-year-old white male student was seen at the University of Chicago Hospitals on Jan. 30, 1962, with frontal headache, mild paresis on the right side, and a systolic murmur.

History. The patient had been seen at Bobs Roberts Hospital when he was 8 months old and again when he was 18 months old. The first admission was for abdominal pain and diarrhea; the second was for an infection of the upper respiratory tract. On both occasions a loud blowing systolic murmur was present diffusely over the precordium, and there was also a faint presystolic murmur noted in the fifth left intercostal space. At 8 months of age the heart was not enlarged on physical examination but was found to be 18 per cent oversized on chest x-ray examination. At 8 months of age roentgenograms of the hands and legs revealed a bone age of 5 months. On auscultation, P_2 was found to be greater than A_2. No cyanosis was described.

The patient was lost to follow-up at the University of Chicago Clinics, but an interim history revealed dyspnea and mild cyanosis after severe exertion as related by the mother. His activity had never been curtailed, and he successfully participated in basketball and football and also held a laboring job for one summer. At 18 years of age he enlisted in the Navy, where twice during training he became cyanotic and lost consciousness after diving into cold water. The diagnosis of "heart trouble" was made and he received a medical discharge.

While attending art school in early January, 1962, he noted frontal headaches; these became increasingly severe but were not disabling. On January 18 he had a grand mal seizure and was admitted to another hospital, where two small seizures were observed, one of which questionably involved the right extremities with clonic contractions. After this the right side was paretic. The cerebrospinal fluid pressure was elevated. The patient was febrile; chloramphenicol was given and the patient was transferred to the University of Chicago Clinics on Jan. 30, 1962.

Clinical course. Physical examination on admission showed a chronically ill male with moderate bilateral papilledema, moderate weakness of the right arm and leg, and hyperactive deep tendon reflexes on the right. Laboratory findings were hemoglobin of 15.6 Gm. per cent, white blood cell count of 12,000 with 69 per cent polymorphonuclear leukocytes, 33 per cent small lymphocytes, 3 per cent monocytes, and 1 per cent eosinophils. Urinalysis was negative except for a trace of albumin. A left carotid angiogram revealed an expanding left parasagittal parietal lesion. Chest x-ray films showed prominence of the pulmonary arteries and pulmonary vasculature but no other focal densities.

One day after admission a left parietal-occipital burr hole was made and 70 c.c. of thick pus was drained from a cerebral abscess. Cultures from the abscess grew beta hemolytic streptococcus, and the patient was treated with chloramphenicol, tetracycline, and penicillin. Thorotrast was used to follow the abscess radiologically, and one subsequent aspiration was necessary before the patient was discharged improved on the twenty-third day of hospitalization, to be readmitted later for cardiac evaluation.

The patient was admitted next in April, 1962. Physical examination showed a blood pressure of 100/75 mm. Hg RAR, pulse of 72 per minute, respirations 12 per minute, and a temperature of 36.2 C. The chest was clear. There was a slight pigeon breast configuration and mild clubbing of the fingers and toes. No thrills were noted and the apex beat was not visible. S_2 was palpable at the left sternal border. S_1 was loud and best heard at the apex. S_2 in the second left intercostal space was accentuated and equal to S_2 in the second right intercostal space and was physiologically split. S_4 was absent. There was

With the participation of Alan Rabinowitz, M.D. (Radiology), Murray Rabinowitz, M.D. (Medicine), and Peter Moulder, M.D. (Surgery). The conference was directed by Seymour Glagov, M.D.

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a Grade 1 midsystolic ejection murmur at the upper left sternal border which did not vary with respiration. No diastolic murmur was heard.

Laboratory data included white blood cell count of 6,900, hemoglobin of 16 Gm. per cent, hematocrit of 55 per cent, platelets 134,000 per cubic millimeter, reticulocytes 0.5 per cent, Na 145 mEq. per liter, K 3.7 mEq. per liter, Cl 108 mEq. per liter, CO_2 28.0 mEq. per liter, pH 7.39, Ca 9.2 mg. per cent, P 4.3 mg. per cent, total protein 5.9 Gm. per cent, 3.7 Gm. per cent albumin, 2.2 Gm. per cent globulin, blood urea nitrogen 8 mg. per cent, cholesterol 160 mg. per cent, esters 105 mg. per cent. Antistreptolysin titer was 1:800 and C reactive protein was negative. Urinalysis was negative. Pulmonary function studies revealed normal ventilation and mechanics. The resting oxygen saturation was 90 per cent, fell to 70 per cent with mild exercise, and rose to 98 per cent with 100 per cent oxygen. Chest x-ray examination revealed 20 per cent cardiomegaly, a diminutive aortic arch, and increased prominence of the pulmonary artery. The electrocardiogram was compatible with right ventricular hypertrophy. The phonocardiogram revealed an ejection click at the base of the heart along with a mid to late systolic murmur. Table I shows the data obtained from cardiac catheterization.

A working diagnosis was made from these data and angiocardiography which showed rapid appearance of radiopaque material in the systemic circulation. The patient was discharged on anticoagulant therapy, Pracoline, Dilantin, and phenobarbital.

He was admitted for corrective surgery in August, 1962. Physical examination was as before. The white blood cell count was 6,000 per cubic millimeter and the hematocrit was 54 per cent. Under Fluothane anesthesia the defect was repaired. Total anesthesia time was 9½ hours, pump time 3 hours. Fifteen minutes after the patient was taken off the *heart-lung bypass, the right heart dilated and* ceased to function. Cardiac massage and intracardiac drugs started it for 3 or 4 minutes after which effective heartbeats were not obtained and the patient died.

Discussion

DR. CASSELS: The more this case is studied the more complex it becomes. A 20 year old man had headaches and it is quite obvious that he had intracranial difficulty. A burr hole was made and purulent material was drained from an abscess. I do not think that this has any real relation to the cardiovascular problem except that this patient was said to have cyanosis and one way the abscess could have some relation to the cyanosis would be by means of paradoxical embolization in the presence of a right to left shunt. Simple abscesses certainly occur in people with intact hearts and in this hospital we see very few cyanotic patients with brain abscesses. This does not seem to hold true however in other institutions and there is a substantial literature on the subject. The incidence is probably low here because of the type of patient seen. In the

Table I. Cardiac catheterization data

Site	*Oxygen content (Vols %)*	*Oxygen saturation early in study (%)*	*Pressure (mm. Hg)*	*Mean pressure*	*Oxygen saturation late in study (%)*
Superior vena cava	14.4	—	—	—	—
Inferior vena cava	15.7	—	—	—	—
Right atrium	14.7	62	6	—	48
Right ventricle	14.7	62	115/–6	—	48
Main pulmonary artery	19.3	80	116/15	82	63
Right pulmonary artery	18.8	—	—	—	—
Ascending aorta	1[illegible].8	92	118/78	80	83
Descending aorta	20.9	—	—	—	81

	Calculated estimated blood flows (liters per minute) Early in study	*Calculated estimated blood flows (liters per minute)* Late in study
Pulmonary blood flow	2.9	1.5
Systemic blood flow	1.8	1.8
Shunt left to right	1.5	0.5
Shunt right to left	0.5	0.5

course of 15 or 20 years a large number of cyanotic patients has been examined but most of them were infants and children

In any event turning to problems which are more pertinent to today's discussion I should like to say at once that I am going to develop a rather fragile formulation

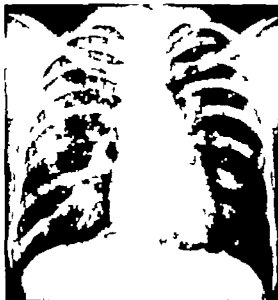




Fig *1* Frontal (*above*) and lateral (*below*) chest films show right ventricular enlargement The main pulmonary artery is prominent and the peripheral pulmonary vascularity is increased

I propose to build a clinical diagnosis on one facet which is not well delineated The diagnosis rests upon the simple problem of whether this patient was cyanotic from birth It is stated that he had dyspnea and mild cyanosis after severe exertion A *heart murmur was noted in childhood* It makes a great difference how you interpret the remainder of the findings and the diagnosis is related to the problem of cyanosis since birth If cyanosis was present since birth a group of alternatives is excluded

Physical examination was not particularly remarkable His pulse was good He breathed quietly The murmur is not helpful in the diagnosis He had a Grade 1 systolic murmur at the upper left sternal border and I presume that this means at about the second left intercostal space The second sound in that area was markedly accentuated The examiners stated that it was physiologically split In the presence of a large blood flow and slower ejection of blood from the right ventricle the pulmonary component of the second sound in the second left intercostal space tends to be delayed and the splitting becomes more obvious With pulmonary hypertension the pulmonary valve closes rapidly and splitting is less evident If the left ventricle was small along with a diminutive aorta interpretation of the split second sound is difficult Furthermore if the phonocardiogram showed a *systolic ejection click its origin* should be sudden distention of a dilated pulmonary artery or aorta but not likely the aorta because of the statement that there was a diminutive aortic arch

In summary this was a 20 year old *man who showed mild clubbing and* was mildly cyanotic however he was able to get into the Navy and when examined in this hospital he had an oxygen saturation which diminished to 70 per cent with mild exercise and rose to 98 per cent with *100* per cent oxygen *He was blue and* again I raise the question of whether this blueness and cyanosis was acquired or whether it was present from birth I do not quite know from the information given Surely the heart murmur was noted *during childhood The hematocrit was* elevated to 55 on one occasion and to 54

on another occasion which fits in with the clinical observation of cyanosis and clubbing and with the low arterial oxygen saturation. I think that we should now see the x-ray films and the electrocardiograms.

DR. BANNIGER: The first chest examination was performed 20 years ago and is said to have shown minimal cardiomegaly. The film is not available. On the recent examination moderate cardiomegaly was present; the heart was approximately 20 per cent oversize according to the nomogram method. Lateral and oblique films suggest right ventricular enlargement. There is no evidence for significant left atrial and ventricular distention. The main pulmonary artery and its major branches on either side are prominent. The peripheral pulmonary vessels are normal. The ascending aorta is in the usual position; evaluation of its size is difficult. The aortic arch cannot be identified (Fig. 1).

DR. CASSELS (interpreting the electrocardiograms): The electrocardiogram shows a prominent S in Lead I, R in Lead III, R in Lead aVR, and R in Lead V_1, which indicate right ventricular hypertrophy. You will note that in Lead V_1 there is no Q wave. There is a good S in Lead V_6 compatible with right ventricular hypertrophy (Fig. 2). In syndromes such as tetralogy of Fallot and some of the transposition complexes in which the right ventricular pressure is high but not above systemic levels, the Q in Lead V_1 is usually absent. In this patient I would assume

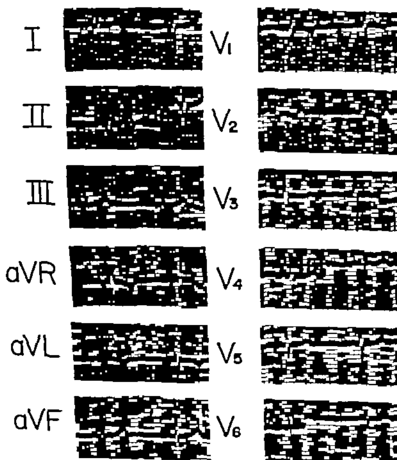


Fig. 2. An ECG on Jan. 31, 1962, reveals a slow sinus rhythm with a heart rate of nearly 50 a minute and a mean axis of about +100 degrees. There is right ventricular hypertrophy. The origin of the sinus bradycardia is not clear. Q is absent throughout the precordial leads.



Fig 3 Frontal (*above*) and lateral (*below*) films selected from a serial angiogram The catheter has entered the ascending aorta from the pulmonary artery Contrast material injected at this point has outlined the ascending aorta and the aortic arch as well as the distal pulmonary artery and its branches The aortic valves are intact and no regurgitation of contrast material into the cardiac chambers is present

that the right ventricular pressure was not above systemic

The data which were obtained by cardiac catheterization are perfectly clear cut If you consider the caval groups the oxygen content is roughly 15 volumes per cent that of the right atrium is about the same that of the right ventricle is about the same and in the pulmonary artery there is a very marked increase in the oxygen content It is much larger than in the case of simple shunts as for instance the usual simple patent ductus shunt A point which I should like to make is the difference in oxygen content between the ascending aorta and the descending aorta since a lower value in the descending aorta is characteristic of a right to left shunt through a patent ductus arteriosus I should like to know whether the sampling was nearly simultaneous or whether a considerable interval intervened since some deterioration in oxygen content could occur with time I think it is important in consideration of the presence of a ductus with pulmonary hypertension

DR RABINOWITZ (interpreting results from cardiopulmonary laboratory) The samples of blood were obtained approximately simultaneously Another set of data taken at an earlier time showed the oxygen content of the ascending aorta to be 21 5 and 21 9 volumes per cent and that of the descending aorta to be 20 9 volumes per cent

DR CASSELS There is a persistent diminution of oxygen content in the descending aorta Everything so far would suggest the possibility of a patent ductus with pulmonary hypertension and reversal of flow There is nothing however mentioned about differential cyanosis His fingers and toes were clubbed If there is marked reversal of flow the toes will all become blue with still more obstruction in the lungs some shunting will occur upward through the aortic arch and complete cyanosis may occur but almost always there is some differential in color A defect at the root of the aorta that caused a communication with the pulmonary artery would tend to show symmetrical cyanosis and a shunt between the ascending aorta and the pulmonary artery above the valve would be suggested There are

at least two points against this diagnosis (1) the possibility that there had been cyanosis since birth and (2) the diminutive aorta I should think that any lesion which caused the aorta to participate in a large flow particularly early in life would not produce a diminutive aorta The great vessels have a reciprocal relationship and if there is great flow through the pulmonary artery the aorta tends to be small This may be the situation in this case You will note that the mean pressures in the great vessels are 82 and 80 mm Hg Therefore we return to the problem of cyanosis associated with a remarkable increase in oxygen in the pulmonary artery He somehow gets this from an arteriolized area and the question is where is this communication Was he blue since early in life? If in the presence of normal or increased pulmonary flow he had been blue since infancy this would almost surely indicate some form of transposition as the most likely diagnosis On the other hand this does not seem to be a simple transposition since patients with that condition are usually quite blue from birth and do not reach the age of 20 years and do not play basketball or football The question is whether this communication between the systemic oxygenated blood and the pulmonary artery is just above the valve or just below the valve On the basis of the information which is presented in the protocol it seems to me to be impossible to say If it were above the valve this might be a truncus or a partial truncus abnormality such as that in the case of an aortic septal defect If this communication were below the valve then I think that this would have been indicated by cyanosis early in life and if so he should have one of the transposition complexes I do not believe that he has a single ventricle This is not a transposition in the usual sense nor a truncus in the usual sense

In the Taussig Bing complex the oxygen content of samples of blood from the pulmonary artery is greater than that of samples obtained from the aorta and is greater than that of any samples of blood except those obtained from the pulmonary veins or the left heart This is not so in this instance His pulmonary artery blood oxygen was 18 8 volumes per cent in one sample and 19 3 volumes per cent in the other The oxygen content of blood in the ascending aorta was 21 8 volumes per cent whereas that of blood in the descending aorta was 20 9 volumes per cent Dr Rabinowitz reported other samples in which the oxygen content of the aortic blood was about 21 volumes per cent By conventional standards this would not be an example of the Taussig Bing complex However the small size of the aorta might favor this diagnosis I should think that the huge flow of blood in the pulmonary artery with an oxygen increase of 4 volumes per cent favors a very large shunt of oxygenated blood and in view of the small size of the aorta the huge shunt and his cyanosis in early life I find it very difficult to place this shunt above the pulmonary and aortic valves Also from the oxygen samples I find it very difficult to

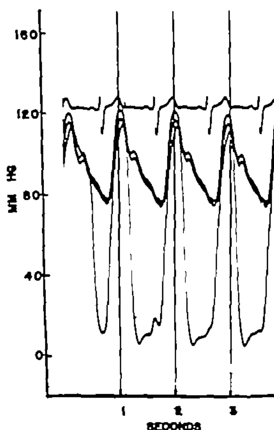


Fig 4 Simultaneous recordings of lead I ECG (*top*) main pulmonary artery pressure and ascending aorta pressure (*superimposed middle curves*) and right ventricular pressure (*lowest curve*)

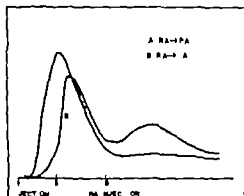


Fig 5 Curve A of the dye-dilution study shows injection into the right atrium with the usual rapid appearance of dye at the distal pulmonary artery This is contrasted with curve *B* where injection into the right atrium allows nearly as rapid appearance of dye at the femoral artery sampling site as in the distal pulmonary artery implying a circulatory shunt bypassing the lung The flatter second peak of curve *B* represents the usual circulation including the pulmonary bed

call it a Taussig Bing syndrome but if it is true that the aorta is really small then I am going to decide in favor of a partial transposition On the basis of the information available I do not think that I can say whether this communication is just above the valves or just below the valves

DR GLAGOV Thank you Dr Cassels Dr Ranniger would you show us the angiogram now

DR RANNIGER During cardiac catheterization the catheter was inserted through the right atrium and right ventricle into the base of the main pulmonary artery There was an obvious connection present between the pulmonary artery and the aorta and it was easy to place the catheter into the ascending aorta With it in this position we injected contrast material Frontal and lateral angiograms show the distended ascending aorta with normal aortic valves (Fig 3) The aortic arch is small Contrast material enters the main pulmonary artery through the defect between aorta and pulmonary artery The latter and its major branches are moderately distended The peripheral pulmonary vessels have a normal appearance The pulmonary valves are intact A patent ductus arteriosus is not demonstrated In summary these angiographic findings provide us with the diagnosis of an aortico pulmonary window

DR CASSELS An aortogram was recorded after injection into the root of the aorta such injection then opacifies the pulmonary artery so that some connection above the valve would be necessary in order for it to do this I did not think that this was a communication between the aorta and the pulmonary artery because this patient had been cyanotic since birth Communications between the aorta and the pulmonary artery usually give rise to pulmonary hypertension and cyanosis later but in fact examination of the world literature for another purpose has revealed about 5 cases of aorta–pulmonary artery communication with cyanosis beginning at birth The information in regard to aortic septal defects is not too clear but pulmonary hypertension should occur more easily since the window defect is larger than a ductus It certainly appears from these angiograms that a communication exists at the point of an aortic septal defect The ascending aorta is large unless this includes part of the pulmonary artery in its projection The aortic arch is small which means that there has been a huge pulmonary flow since birth The 4 volumes per cent difference is greater than any usual shunt seen in a supravalvular communication The essential points necessary

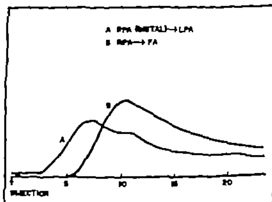


Fig 6 Curve A shows injection into the distal right pulmonary artery and sampling from the distal left pulmonary artery The rapid appearance of dye back in the pulmonary system implies a left to right shunt in the heart or great vessels at the base Curve *B* shows injection into the right pulmonary artery and sampling from the femoral artery

for a clinical diagnosis remain as questions Was the patient blue in early infancy? Was there a continuous murmur at any time? The early history is not clear

DR RABINOWITZ On cardiac catheterization the catheter was placed into the right ventricle and into the pulmonary arteries Severe pulmonary hypertension was found to be present The catheter passed rather easily from the pulmonary artery into the ascending aorta the arch of the aorta and into the descending aorta so that the diagnosis of a window between the aorta and pulmonary artery was made The oxygen saturation of blood taken from the various heart chambers indicated a prominent step up in the oxygen saturation of pulmonary arterial blood there being no step ups at the ventricular arterial level Thus a significant left to right shunt was present Early in the studies the oxygen saturation of blood in the ascending aorta was 92 per cent indicative of only a small to moderate right to left shunt Later in the study hemodynamic changes indicative of increasing pulmonary vascular resistance and decreasing systemic resistance appeared The patient developed increasing peripheral arterial desaturation with the saturation of samples of arterial blood falling to 80 per cent Initially a predominantly left to right shunt with a relatively small right to left shunt was present Later in these studies which were quite prolonged the flows through the defect appeared to be balanced with almost equal bidirectional shunts being present This is quite important in reference to subsequent surgery Fig 4 shows simultaneously recorded pressures from the right ventricle pulmonary artery and ascending aorta demonstrating the equal systolic pressures in the pulmonary artery aorta and right ventricle Figs 5 and 6 show indicator-dilution studies that demonstrate the abnormal pathway of the blood flow In Fig 5 curve *B* injection into the right atrium with sampling from the femoral artery results in a very rapid appearance of dye at the femoral artery sampling site This represents a right to left shunt at or distal to the right atrium bypassing the pulmonary bed A similar early appearance is obtained when injection is made into the right ventricle and main pulmonary artery but is not present when injection is made into the distal right pulmonary artery (Fig 6 curve *B*)



Fig 7 Aorticopulmonary septal defect with operative intervention Anterior view of the heart *A* With aorta laid open *B* With the pulmonary trunk laid open Arrows point to incisions in aorta and pulmonary trunk



Fig. 11. These medium sized pulmonary arteries show severe medial and intimal thickening. Hematoxylin and eosin; magnification X15.

distal to the site of shunting. The later peak represents blood passing through the normal pathways into the pulmonary artery and lung capillaries and then to the left atrium, left ventricle, and the peripheral arteries. Also seen in Fig. 6, curve B, with injection into the right pulmonary artery and sampling from the right femoral artery, is the gradual disappearance of dye that indicates a large central left to right shunt.

In Fig. 6, curve A, injection of dye was into the distal right pulmonary artery with sampling from the distal left pulmonary artery. Normally, the dye must pass through the systemic circulation, thus taking many seconds to reappear at the sampling site. The rapid appearance of dye in this case indicates a left to right shunt. Subsequently, the sampling catheter was withdrawn to the right ventricle and injection was made into the right pulmonary artery. This failed to demonstrate the early appearance of dye, thus localizing the left to right shunt at the level of the pulmonary artery.

In conclusion, the hemodynamic data demonstrated a defect between the aorta and pulmonary artery with the pressures in the pulmonary artery and right ventricle at systemic levels and evidence of bidirectional shunting of blood. The predominant left to right shunt demonstrated earlier in the procedure was to us a hopeful sign which indicated that the pulmonary arteriolar pressure was not yet fixed.

DR. MOULDER: By usual criteria, the patient's condition was inoperable and should be considered more from the experimental point of view. We had pretreated this patient with decoagulation and Priscoline for a shorter period of time than we usually do. I think that it was about 3 months in this instance, and then we had hoped to be able to do a test occlusion, but it was such an enormous communication that there was no way of clamping it to set up a test occlusion. The procedure was going quite well, so that we went ahead and did close the window. Sudden right heart failure occurred not long after the patient was taken off bypass, a development unfortunately characteristic of patients with severe pulmonary hypertension.

Pathologic anatomy

DR. LEV: Dr. Straus, who performed the autopsy, has gone over the postmortem findings with me, and I have studied the heart and lungs. The anatomic data may be said to supplement the clinical data

which have been so well presented by Dr Cassels and his colleagues There was an aorticopulmonary septal defect combined with a patent ductus arteriosus Perhaps in the course of our discussion we will shed some light on the reason for the death of the patient First we show the effects of surgery that is the aorta and pulmonary trunk have been separated (Fig 7) You heard Dr Moulder state that he closed the aorticopulmonary septal defect Fig 7 A shows the incision on the aortic side It is a fairly long incision and indicates the long opening which had been present The opening of the ductus arteriosus is above It has recently been surgically ligated On the pulmonary side we see the incision (Fig 7 B) A prosthesis has been put into the pulmonary artery defect The basic pathology then is an aorticopulmonary septal defect and patent ductus arteriosus

The effects of this combined defect upon the heart can now be seen The right ventricle is enlarged and its wall is thickened We know that after the operation there was dilatation of the heart and hence we can assume that before the operation we were dealing with a more or less normal sized chamber that had a thickened wall due to increased muscle mass or what I call pressure hypertrophy of the right ventricle There is thickening of the endocardium of this chamber which indicates prolonged damage We do not know exactly what factors were involved in thickening of the endocardium except that they were probably related to some type of turbulence The pulmonary valve shows markedly advanced hemodynamic change The right atrium is thickened and the endocardial lining also shows considerable thickening The tricuspid valve shows marked hemodynamic change On the left side of the heart is a small atrial septal defect of the fossa ovalis type and we learn clinically that this is unimportant hemodynamically In looking at the left side of the heart I cannot say definitely whether we are dealing with a slight hypertrophy of the left atrium and left ventricle or a normal left atrium and left ventricle Perhaps there is slight hypertrophy Considerable hemodynamic changes in the mitral valve indicate a turbulence of flow in this region and there is some thickening of the endocardium of the left atrium and left ventricle In summary as we review the findings in the heart we see that we are dealing with pressure hypertrophy



Fig 7B The small pulmonary artery is greatly narrowed probably representing old occlusion with rechannelization Hematoxylin and eosin magnification ×180



Fig 8C The field is bisected by the organizing margin of a pulmonary infarction Within the infarcted area necrotic alveolar wall contain iron calcium deposition A markedly thickened small pulmonary artery is evident at the lower left Magnification ×40

of the right ventricle and the right atrium I do not know whether the thickening of the latter pertains directly to pressure As for the left side we equivocate in saying that we have either a normal left side or perhaps a slightly hypertrophied and dilated left side This correspoods of course to the clinical data in which we dealt with aorticopulmonary septal defect with patent ductus arteriosus with probably some reversal of flow in the ductus and marked pulmonary hypertension with probably very little increased flow into the left side This is consistent with the comments of Dr Rabinowitz

What was the status of the patient as he underwent surgery Here we are looking for evidence of chronic passive hyperemia of the liver and spleen There are no findings which indicate that the patient was in congestive failure at the time of operation We are dealing with pressure hypertrophy of the right ventricle which means that there has been either a considerable flow into the lung bed and/or occlusive vascular changes going on in the lungs which may account for the right ventricular hypertrophy Hence the lung is a very important factor in the life and death of this patient

Grossly we note that there is thickening of all the vessels on the cut surface Microscopically muscular arteries of medium size small arteries and arterioles all show marked thickening with proliferation (Figs 8A 8B 8C) I cannot tell from ordinary stains how much media and how much intima are involved in the narrowing but we are dealing here with severe occlusive phenomena of the pulmonary vascular bed We can actually see the fragmentation of the elastin The effect on the lung itself is seen by the fibrosis present

In the pulmonary parenchyma are several firm focal dark red lesions which on microscopic examination are shown to be areas of pulmonary infarction now partially organized with fibrotic peripheral zones and central hemorrhagic necrosis There is focal iron calcium deposition in necrotic alveolar walls (Fig 8C)

In summary the old changes in the lungs indicate that there must have been a considerable increase in blood flow through these organs and that relative to this marked flow pulmonary hypertension chronic passive congestion and focal infarction developed The hyperkinetic pulmonary hypertension caused secondary



Fig. 9. This is subendocardial and superficial myocardial hemorrhage representing acute preterminal changes. Magnification ×105.

pulmonary vascular changes, an increase in pulmonary resistance, and further increased pressure in and work for the right ventricle.

There were also acute changes in the lung which correlated with acute changes in other parts of the body, all pointing to the possible effect of surgery itself. The lung showed marked pulmonary edema. We see acute degenerative changes of collagen. In the liver there was evidence of acute degenerative changes in the central zones and an increase in fat throughout the parenchyma of the liver. In the kidney there was fat in the proximal convoluted tubules and perhaps in the distal tubules. In the adrenal glands there were hemorrhages in the cortex as well as necrosis of some of the cortical cells. Various small hemorrhages were present throughout many organs including the spleen, myocardium, and endocardium (Fig. 9). A vessel in the myocardium showed degeneration of collagen in the adventitia with some proliferation of cells. I am struck with the concept of something acute being present and would like to say that the death of this patient was associated with an acute phenomenon. We do not know exactly what it was nor its relationship to the operative intervention.

In summary, this was a case of aorticopulmonary septal defect combined with patent ductus arteriosus, pulmonary hypertension, pulmonary fibrosis, operative intervention, and death.

DR. GLAGOV: Thank you, Dr. Lev. Now, Dr. Moulder, Dr. Ranniger, Dr. Rabinowitz, are there any questions you would like to ask Dr. Lev before we let Dr. Cassels conclude the Conference?

DR. RANNIGER: Dr. Lev, how large was the patent ductus?

DR. LEV: I was told that it was about 0.5 cm. in diameter.

DR. MOULDER: I remember nothing that would indicate that we had a poor cardiopulmonary bypass except for one thing. We did not suspect a patent ductus which allowed a shunting of perfused blood into the surgical field, producing a reduced systemic perfusion. The ductus was sutured with about 10 minutes of low perfusion.

DR. LEV: This helps to explain the acute changes.

DR. MOULDER: I should like to ask about the changes in the heart because we did not cross clamp the aorta. We put a partial



Fig 8C The field is bisected by the organizing margin of a pulmonary infarction Within the infarcted area necrotic alveolar walls contain iron calcium deposition A markedly thickened small pulmonary artery is evident at the lower left Magnification ×40

of the right ventricle and the right atrium I do not know whether the thickening of the latter pertains directly to pressure As for the left side we equivocate in saying that we have either a normal left side or perhaps a slightly hypertrophied and dilated left side This corresponds of course to the clinical data in which we dealt with aorticopulmonary septal defect with patent ductus arteriosus with probably some reversal of flow in the ductus and marked pulmonary hypertension with probably very little increased flow into the left side This is consistent with the comments of Dr Rabinowitz

What was the status of the patient as he underwent surgery? Here we are looking for evidence of chronic passive hyperemia of the liver and spleen There are no findings which indicate that the patient was in congestive failure at the time of operation We are dealing with pressure hypertrophy of the right ventricle which means that there has been either a considerable flow into the lung bed and/or occlusive vascular changes going on in the lungs which may account for the right ventricular hypertrophy Hence the lung is a very important factor in the life and death of this patient

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Fundamentals of clinical cardiology

The prognosis of acute rheumatic fever

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Investigations of prophylaxis against recurrent attacks of rheumatic fever have enabled us to follow a large population of children and adolescents at monthly or bimonthly intervals, using techniques that increase the precision and objectivity of clinical examination. The 441 patients who comprise this population had had acute rheumatic attacks during the years 1950-1957 and were afterward admitted to an outpatient epidemiologic research clinic organized specifically for this study. Their follow-up examinations in the clinic began in 1954, and we have recently reported[1] the streptococcal infections, rheumatic recurrences, and changes in cardiac status detected during the outpatient observations of 1954-1960.

While those long-term observations of the *sequelae* of rheumatic fever were in progress, we performed a separate investigation[2-4] of the clinical patterns present during the *acute phase* of rheumatic attacks. The intensive study of acute attacks was performed in a different population consisting of 369 patients hospitalized with rheumatic episodes during 1958-1960. Clinical analysis of the acute illnesses of those patients demonstrated at least two critical features of biologic behavior in rheumatic fever. (1) The acute clinical severity of arthritis and of carditis were generally inversely proportional: rheumatic fever was likely to bite the heart when it licked the joints, and to lick the heart when it bit the joints. (2) After the acute attack subsided, patients treated early had less residual heart disease than those treated late, but the difference could not be definitely attributed to prompt therapy. Arthritic patients had sought treatment quickly for their symptoms but initially had less carditis than the nonarthritic group. Compared with arthritic patients, those without arthritis had a greater prevalence and severity of carditis but had come to treatment later because their insidious cardiac manifestations often took longer to reach a symptomatic severity that evoked medical aid.

The demonstration of these clinical patterns during rheumatic attacks in the 1958-1960 population was achieved through new techniques of data analysis. These techniques divided and classified the acutely ill patients according to specific clinical as-

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pects of symptoms and signs in addition to the conventional classifications based on laboratory data and such nonclinical personal properties as age race and sex The new clinical classification techniques were developed for studying the 1958 1960 population but could *not* be used to correlate the ultimate sequelae of rheumatic fever with the acute events because the duration of subsequent follow up in that population was necessarily brief The desired long term correlations however could be performed for the earlier 1950 1957 population in which extensive cardiac follow up data are available The long term data of the 1950 1957 population have already been correlated with the status of the patients after the acute attack[3] but have not been analyzed in relation to the clinical events present *during* the antecedent acute rheumatic episodes The present work is intended for this correlative analysis and will report the manifestations clinical interrelationships treatment and long term cardiac sequelae of acute rheumatic fever in that population

Clinical material and methods

During 1950 1957 the 441 children and adolescents of this study had attacks of acute rheumatic fever that fulfilled the modified Jones diagnostic criteria[4] The index attack defined as the one that brought each patient initially to our observation was a first episode of rheumatic fever for 271 patients and a recurrence for 170 During the acute attacks the patients were treated by many different physicians and at many different hospitals Some patients were seen at Irvington House during the early stages of the illness most were sent to Irvington House for further inpatient care after treatment had been instituted or stopped a few were referred for outpatient care after the acute attack had subsided

The events that occurred during the acute attacks in these patients were not observed or recorded with the precision of method used in a research project Surveillance of this population with scrupulous research techniques did not begin until after the acute attacks when the patients were assembled and admitted to the special outpatient epidemiologic clinic established for this study[4] Consequently the data of the acute rheumatic episodes represent observations interpretations and decisions made by many different physicians who used many different standards and criteria As discussed later such defects are a necessary feature of the collection of a rheumatic population large enough for statistical analysis These disadvantages in the initial uniformity of examination are outweighed by the advantages of the improvements developed in the techniques of long term follow up observations The population described here represents the largest group of rheumatic patients followed at frequent intervals for sustained lengths of time at a single clinic by examiners who used objective precise methods for laboratory detection of streptococcal inflammation and clinical recognition of cardiac changes

All of the available data for the acute index attacks and (when appropriate) previous attacks of these patients were obtained by diligent communication with the referring and previous medical sources Some of those data had been acquired during or shortly after the rheumatic episodes of 1950 1957 other data were solicited later from the medical records of the referring hospitals and physicians The outside information was added to the inpatient and outpatient records of Irvington House to form a complete chronology of each patient s rheumatic course from onset to its most recent state The criteria and classifications used for coding the index attacks are noted below

During the acute attack a patient was designated as having had *arthritis* if any joint had been described as red hot swollen or objectively tender or if the term polyarthritis had been used descriptively without further specification If a patient complaining of pain in the joints did not have any of these arthritic features when examined the condition was classified as *arthralgia* The diagnoses of *chorea* *erythema marginatum* and *subcutaneous nodules* were accepted when recorded elsewhere as present when made from observations at Irvington House the standards of diagnosis were those of the Jones criteria[4]

The cardiac aspects of the acute attacks were classified according to the four clinical

features of cardiac involvement noted in the modified Jones criteria (1) significant murmurs (2) significant cardiac enlargement (3) congestive heart failure and (4) pericarditis The diagnostic specifications for each of these categories have been described in considerable detail elsewhere and will not be repeated here By these specifications patients were designated as having either definite possible or no involvement of the mitral or aortic valves and the corresponding murmurs were indicated as systolic or diastolic (or both) Cardiac enlargement and congestive heart failure were each classified as definite or doubtful doubtful interpretations were considered to be negative in the analyses reported here Pericarditis was diagnosed on the basis of a rub or effusion but not (for reasons noted elsewhere) according to electrocardiographic evidence only Prolongation of the P R interval was noted for analysis but was not used per se as evidence of carditis

Patients were classified as having *severe carditis* during the acute attack if they had cardiac enlargement or congestive heart failure or both regardless of other cardiac manifestations Patients were classified as having *mild carditis* if they had a significant murmur but not cardiomegaly or decompensation Patients were considered to have *possible carditis* if a possibly significant murmur was the most definite evidence of cardiac involvement Unless otherwise specified in the analyses reported here the unmodified term carditis refers to patients with either possible mild or severe carditis as just defined All other patients were designated as having *no carditis* (These designations did not make use of pericarditis in classifying the presence or severity of carditis As will be noted later all but 2 of the patients with pericardial rubs had other clinical evidence of cardiac involvement in the 2 patients with no other evidence the rub later disappeared leaving no clinically detectable rheumatic heart disease)

For each patient s acute attack a *pretreatment interval* was calculated This interval was the length of time elapsed between onset of symptoms attributable to the rheumatic fever and the beginning of anti inflammatory therapy with salicylates or steroids In patients who had received none of these agents the onset of therapy was considered to be the date at which bed rest began under medical supervision The anti inflammatory treatment had been given in many varieties of drug dosage and duration For the analysis here treatment was classified according to the first therapeutic agent(s) employed and was designated as salicylate steroid or combined The treatment was regarded as combined when salicylates and steroids were begun simultaneously or when the second agent was added within 5 days after the first was started The anti inflammatory treatment was marked as none if the patient had received neither salicylates nor steroids for a period of more than 5 days In some patients particularly those with chorea as the only clinical manifestation the pretreatment interval could not be determined and was marked as unknown In a few patients the therapeutic agents employed (if any) were unknown or uncertain The dosage and duration of anti inflammatory agents had been given in too many variations for useful correlation in the analysis reported here

After completion of the acute attacks the patients were admitted to the out patient research clinic where they were examined at monthly or bimonthly intervals while receiving continuous antistreptococcal prophylaxis For the first 2 years of operation of the clinic the follow up examinations at each patient s repeated visits were performed in the traditional manner i e the physician received the patient s medical record inspected the record and then examined the patient It later became apparent that crucial auscultatory observations might be biased by this procedure Therefore the sequence of examination was changed so that the physician performed each auscultation *before* he inspected the medical record After his initial impressions were formed he could then compare his observations with those already recorded previously Whenever his interpretations differed from those already recorded thus suggesting a change in valvular status of the patient an auscultatory team examination was performed For this process all of the 4 to physicians in attendance at the

examined the heart blindly without prior knowledge or advance discussion of the cardiac findings.

This type of objectivity in examination led to increased precision and reproducibility of acoustical observation and to the development of the rigorous criteria cited elsewhere[7,8] for distinguishing pathologic from physiologic cardiac noises. The criteria were based on the distinctions provided by the detailed descriptions of the various sonorous properties of cardiac noises. As the study progressed, for example, the designation of mitral regurgitation required fulfillment of specific criteria more comprehensive than those used (or applicable to the recorded data) in the acute index attacks. The new criteria were based not merely on loudness, transmission, pitch, and quality of the murmur, but also on its thoracic site of maximum loudness, time of onset, duration, and response of apical intensity to respiratory and thoracic maneuvers that affected the vertical position of the heart. In addition to the improvements in criteria provided by the augmented acoustic descriptions, the employment of multiple objective examiners had two major advantages: (1) changes in valvular status could represent the consensus of a group of different observers rather than the auscultatory idiosyncrasies of one or two physicians; (2) there was little or no likelihood of occurrence of the phenomenon[9] in which a diastolic murmur is present but remains unheard for many years until it is finally detected and erroneously considered to be new.

The objectivity and precision of x-ray interpretation were also improved by a similar blind technique in which the roentgenologist examined each film and formed an initial impression *before* he looked at clinical data or at previous films and their written interpretations. This procedure led to more precise assessment of cardiac size and to greater consistency and reproducibility of interobserver and intraobserver interpretations. The specific criteria for separation of normal and abnormal shadows were improved as the study progressed.[10]

Of the original 441 patients, only 44 failed to complete at least 5 years of observation. Five of those died, and the others had moved away or dropped out of the clinic. (The initial composition and cardiac sequelae of this drop-out group are noted elsewhere[2] and did not differ in any significant proportion from those of the group of patients who remained in the clinic.) For the patients who continued under long-term observation, the final status for the analysis reported here was recorded during the examinations of late 1961 and early 1962. For all 441 patients, the mean follow-up time from the index attack to final status was 7.8 ± 2.4 years. With removal of the 44 drop-out patients, the mean duration of follow-up for the other 397 patients was 8.3 ± 1.5 years. (The ± values are standard deviations from the mean.) All follow-up examinations were performed by our clinic staff, and each patient was classified as having definite, questionable, or no rheumatic heart disease.

Results

I. Presenting manifestations of the acute attacks: comparison of populations (Table I). Table I indicates the occurrence and severity of carditis during the acute attacks of the 1950-1957 population and relates these features to the types of presenting symptoms. The table simultaneously indicates the same data, as already observed and reported elsewhere,[4] for the acute first attacks of the 1958-1960 population. In almost all categories, the findings in the two populations are quite similar. In the current 1950-1957 series, carditis occurred in 129 (48 per cent) of the 271 patients and was severe in 31 (11 per cent). The occurrence and severity of carditis was distinctly related to the types of presenting symptoms, a feature also noted in the previously analyzed series. Carditis was found in 17 per cent of patients with chorea and no joint symptoms, in 39 per cent of those with arthritis, in 92 per cent of those with arthralgia, and in 95 per cent of those who were neither choreic nor arthropathic. Severe carditis had a similar ascending occurrence, ranging from 0 per cent in the "pure" chorea group to 47 per cent in patients with no "rheumatic" or choreic symptoms. Both of these progressive increases in the prevalence of carditis with decreasing severity of nonchoreic

arthropathy are statistically significant at the level of $P < 0.01$

The data of the second population as studied here thus confirm the observations made on the first population showing that the severity of arthritis and carditis are often inversely related in acute rheumatic fever. Moreover the proportionate distribution of clinical features in the two populations is similar enough to suggest that acute rheumatic fever (as seen in these referred patients) had not greatly changed its characteristics or severity during the decade in which the patients of two populations had their first attacks

II Long term cardiac sequelae in relation to events of the acute attacks

A RESIDUAL HEART DISEASE DEATHS AND INITIAL CARDIAC STATUS (TABLE II) At the last examination of the 441 patients in this population rheumatic heart disease was absent in 295 questionable in 9 and definitely present in 135 Twelve patients had died of rheumatic heart disease (A thirteenth death was by automobile accident in a patient who had no heart disease at the time of his final medical examination) Rheumatic heart disease in living or dead patients was thus present in 33 per cent of the entire population This proportion was strikingly different however for each of the four categories of initial cardiac involvement The percentage of residual heart disease ranged from 0 to 9 per cent in patients with no or possible carditis to 55 and 87 per cent respectively in those with mild and severe carditis

Of the 12 patients who died of rheumatic heart disease 11 had severe carditis initially The acute attacks and subsequent courses of these 12 patients are described in detail elsewhere It may be noted here that only one of the patients had evidence of active rheumatic inflammation during the follow up period The acute inflammation of that patient was a recurrent episode of rheumatic fever In all other patients cardiac deterioration and death occurred with no evidence of persistent or recurrent rheumatic activity

B PRETREATMENT INTERVAL TYPE OF TREATMENT SEVERITY OF CARDITIS AND RESIDUAL HEART DISEASE IN FIRST ATTACKS (TABLE III) The time at which patients

Table I Presenting manifestations in two different populations of young patients with first attacks of acute rheumatic fever

Manifestations and severity of joint symptoms on presentation	*Population and time of acute attack*	*Total number of patients*	*Number and percentage of patients with*	
			Carditis all type	*Severe carditis*
Chorea no joint symptom	1958–1960	12	3(25[illegible])	0(0[illegible])
	1950–1957	6	1(17)	0(0)
Arthritis	1958–1960	209	59([illegible]8)	6(3)
	1950–19[illegible]7	221	87(39)	18(8)
Arthralgia	1958–1960	25	24(96)	8(3[illegible])
	1950–1957	25	23(9[illegible])	4(16)
No joint symptoms or chorea	1958–1960	29	29(100)	16(55)
	1950–1957	19	18(95)	9(47)
Total	1958–1960	[illegible]5	115(4[illegible])	30(11)
	1950–1957	271	129(48)	31(11)

Numbers in parentheses are percentages.

Thirteen of these patients later developed chorea. [illegible] Three of these patients later developed chorea. [illegible] Table III for the number of patients of each group [illegible] 1958–1960 [illegible] who developed chorea [illegible]

come to treatment in acute rheumatic fever and the effects of treatment are best assessed in patients with *first* attacks of the disease. Patients who have had one or more known attacks are not well suited to such appraisals of natural history and therapy. The pretreatment time interval of recurrent rheumatic attacks is often distorted because the patients are already under medical surveillance or particularly alert to new symptoms before the recurrent attack. Moreover, the evaluation of therapeutic cardiac effects in rheumatic recurrences is impeded by the tendency of valvular damage to remain absent in the recurrent episodes of patients previously free of it[1] and by the difficulty of appraising new cardiac deterioration in patients who already had cardiac damage previously. Consequently, the evaluation of therapy and of pretreatment interval in this study is confined to the 271 patients whose index attack was a first episode of acute rheumatic fever.

Table II. Initial cardiac status and residual rheumatic heart disease after acute rheumatic fever

Initial cardiac status	Number of patients	Final cardiac status: number of patients with				Percentage of patients with RHD alive or dead
		No RHD	? RHD	RHD alive	RHD dead	
No carditis	181	180*	1	0	0	0
Possible carditis	44	38	2	4	0	9
Mild carditis	141	57	6	77	1	55
Severe carditis	75	6	4	54	11	87
Total	441	281	13	135	12	33

*One patient [illegible] RHD [illegible]
RHD: Rheumatic heart disease.

Table III. Severity of carditis, pretreatment interval, treatment, and residual heart disease in 271 patients with first attacks of rheumatic fever

Pretreatment interval	1st inflammatory treatment	No carditis	Possible carditis	Mild carditis	Severe carditis	Total
0-2 wk.	Salicylate	0/63	0/11	7/24	6/7	13/105
	Steroid or combined	0/34	1/8	6/16	8/11	15/69
	None	0/4	0/2	0/4	1/1	1/11
Subtotal		0/101	1/21	13/44	15/19	29/185
3 wk. or more	Salicylate	0/5	—	3/4	3/4	6/13
	Steroid or combined	0/10	0/1	3/7	4/4	7/22
	None	0/4	—	2/5	—	2/9
Subtotal		0/19	0/1	8/16	7/8	15/44
Unknown or uncertain	Salicylate	0/14	0/2	1/3	2/2	3/21
	Steroid or combined	0/6	0/1	0/1	—	0/8
	None	0/2	0/4	5/5	2/2	7/13
Subtotal		0/22	0/7	6/9	4/4	10/42
Total	Salicylate	0/82	0/13	11/31	11/13	22/139
	Steroid or combined	0/50	1/10	9/24	12/15	22/99
	None	0/10	0/6	7/14	3/3	10/33
Total		0/142	1/29	27/69	26/31	54/271

Denominators list the number of patients in each category; numerators list the number who had residual heart disease.

The interval between onset of symptoms and of treatment was known for all but 42 of the 271 patients. Of the 185 patients who came to treatment within 2 weeks after onset of symptoms only 63 (34 per cent) had definite carditis. By contrast, definite carditis was present in 24 (55 per cent) of the 44 patients with a pretreatment interval longer than 2 weeks. The difference is significant at $P < 0.02$ ($\chi^2 = 5.5$). This same phenomenon was also noted in the acute attacks of the previous population[3] and was explained by the observation that patients with arthritis usually seek treatment promptly but have little or no initial carditis.

Residual rheumatic heart disease (in life or at the time of death) occurred in none of the 142 patients who had no carditis when first encountered, in only one of the 29 patients with possible carditis, and in 26 of the 31 patients with severe carditis. In these three cardiac categories the presence or absence of residual heart disease was unaffected by the time or type of treatment.

In the 69 patients who had mild carditis residual heart disease occurred in 27 (39 per cent): it occurred in 13 (30 per cent) of the 44 patients treated within 2 weeks, in 8 (50 per cent) of the 16 treated beyond 2 weeks after onset of symptoms, and in 6 (67 per cent) of the 9 patients in whom the pretreatment interval was unknown. Treatment in the mild carditis category was followed by residual heart disease in 11 (35 per cent) of the 31 patients who received salicylates, in 9 (36 per cent) of the 24 treated who had steroids or combined therapy, and in 7 (50 per cent) of the 14 who received no anti-inflammatory treatment. None of these differences is statistically significant.

These data thus demonstrate that the long term cardiac outcome of first attacks of acute rheumatic fever did not appear to be significantly affected by the type of anti-inflammatory treatment or by the promptness with which treatment was given. The biologic behavior of the disease and the general cardiac state of the patient at the onset of treatment seemed to be the most pertinent features in the ultimate prognosis.

These results also demonstrate how erroneous conclusions may be reached when therapeutic data are analyzed statistically without appropriate attention to the clinical nuances of the disease. For example, residual heart disease was present in 29 (16 per cent) of 185 patients with a pretreatment interval of 2 weeks or less and in 15 (34 per cent) of 44 patients in whom this interval was more than 2 weeks; residual heart disease occurred in 22 (16 per cent) of 139 patients treated with salicylates and in 22 (22 per cent) of 99 patients treated with steroids or combined therapy. In the first instance of comparison the difference between the percentages is statistically significant at $P < 0.01$ ($\chi^2 = 6.6$); in the second instance, $P < 0.2$ ($\chi^2 = 1.1$).

Considered in biologic detail, however, neither of these differences is clinically meaningful, regardless of its statistical probability. The apparently better cardiac results of early treatment and of treatment with salicylates are due to the inclusion in each category of many patients who initially had no carditis. The total clinical data, when appropriately subdivided for initial cardiac stage, show no advantage of steroids over salicylates (or vice versa) and no advantage of prompt over late therapy in reducing residual heart disease in patients with comparable degrees of carditis in first attacks.

C. PROGNOSTIC FEATURES IN ACUTE ATTACKS. The foregoing data have demonstrated that the natural course of the acute disease appeared to determine the manner and state in which it was found, and that the subsequent course was not significantly altered by the time and type of treatment. In the data of this section the overt clinical features of the acute disease are correlated with its ultimate outcome.

Some patients with rheumatic fever come to medical attention because of joint symptoms or chorea, or both. Other patients may have no choreic or rheumatic manifestations and instead seek medical help for fever or for clinical features of congestive heart failure. In yet other patients the disease is discovered almost by accident, as a significant murmur encountered during a general examination performed for a symptom or purpose not related to rheumatic fever.

The previous section and earlier stud

Table IV Clinical presentations types of carditis and residual rheumatic heart disease after initial and after recurrent attacks of acute rheumatic fever

Arthropathic or choreic manifestations of acute attacks	Patients with first attacks				Patients with recurrent attacks			
	No carditis	Possible or mild carditis	Severe carditis	Total	No carditis	Possible or mild carditis	Severe carditis	Total
Arthritis only	0/131 (0)	14/60 (?3)	14/17 (82)	28/208 (?6)	0/31 (0)	(1)27/46 (59)	(3)15/17 (88)	(5)42/94 (45)
Arthritis and chorea	0/3 (0)	?/9 (2?)	1/1 (100)	3/13 (23)	0/2 (0)	3/6 (50)	1/2 (50)	4/10 (40)
Chorea only	0/6 (0)	2/3 (67)	——	2/9 (22)	0/5 (0)	3/5 (60)	——	3/10 (30)
Chorea and arthralgia	0/2 (0)	0/1 (0)	——	0/3 (0)	——	1/1 (100)	1/1 (100)	2/2 (100)
Arthralgia only	——	5/18 (?8)	(1) 3/4 (75)	( )8/22 (36)	——	9/14 (64)	( )11/11 (100)	(4)20/25 (80)
None	——	5/7 (71)	( ) 8/9 (89)	( )13/16 (81)	0/1 (0)	11/15 (73)	(1)11/13 (85)	(1)22/29 (76)
Total	0/14? (0)	?8/98 (28)	(1)?6/31 (84)	(5)54/271 (20)	0/39 (0)	(1)54/87 (6?)	(4)39/44 (89)	(5)93/170 (35)

Th p [illegible] the [illegible] only major manifestation of [illegible] fever
D [illegible] the number of patients [illegible] each category [illegible] the total number [illegible] with [illegible] rheumatic heart disease Parentheses indicate the percent [illegible] superscript numbers [illegible] the number of patients dead of rheumatic heart disease

ies[3,4] have demonstrated that these patterns of acute clinical manifestation are not mere fluctuations in symptoms and signs but are useful indices of biologic behavior of the acute disease The data of this section carry these analyses further and demonstrate that the occurrence of residual heart disease is also directly correlated with other clinical features besides those of the acute cardiac manifestations

Table IV cites the types of clinical presentations of acute rheumatic fever in patients with first attacks and with recurrent attacks These modes of presentation are then correlated with the occurrence and severity of carditis in each clinical group and with the incidence of residual heart disease in each category The correlations are analyzed below

1 First Attacks vs Recurrent Attacks In each comparable clinical category of Table IV the patients with recurrent episodes of rheumatic fever had more residual heart disease than did those with first attacks This finding however does not imply that the recurrent attacks necessarily brought heart disease to patients previously free of it Work reported elsewhere[1,4] has demonstrated that these results arise instead because patients with heart involvement are more likely to develop recurrent attacks than are patients free of cardiac damage This tendency is demonstrated by the finding that 142 (52 per cent) of the 271 patients with first attacks were initially free of carditis compared with 39 (23 per cent) of the 170 patients with recurrent attacks The difference is statistically significant at P < 0 001 (χ = 36 2) Regardless of whether they were undergoing first attacks or recurrences however all of these noncarditic patients remained free of residual heart disease thereafter At the other end of the carditic scale 31 (11 per cent) of the 271 patients with first attacks initially had severe carditis compared with 44 (26 per cent) of the 170 patients with recur

rences. The difference is statistically significant at $P < 0.001$ ($\chi = 14.4$). Among these patients with severe carditis the amount of residual heart disease was essentially the same after first attacks (84 per cent) as after recurrences (89 per cent) ($\chi = 0.06$, $P = 0.8$).

The existence of rheumatic attacks prior to the index attack seemed to have significant effects on residual heart disease only in patients with possible or mild carditis in the index attack. Despite comparable similarity of cardiac involvement in patients with possible or mild carditis, residual heart disease remained in 28 (28 per cent) of 98 such patients with first attacks and in 54 (62 per cent) of the 87 patients with recurrent attacks. This difference is statistically significant at $P < 0.001$ ($\chi = 19.6$).

ARTHRITIS
CARDITIS
0/131 (0 %)
14/60 (23 %)
5/7 (71 %)
SEVERE CARDITIS
8/9 (89 %)
2/9 (22 %)
0/3 (0 %)
0/8 (0 %)
0/13 (0 %)
5/18 (28 %)
THIS SUBSET IS DIAGNOSTICALLY NOT RHEUMATIC FEVER
CHOREA
ARTHRALGIA

ARTHRITIS — CARDITIS — ARTHRALGIA — CHOREA — SEVERE CARDITIS

Fig. 1. The clinical spectrum and prognosis of acute rheumatic fever. This Venn diagram borrowed from the techniques of symbolic logic shows the distribution of various clinical properties and the corresponding residual rheumatic heart disease in 71 patients with first attacks of acute rheumatic fever. The four large circles contain sets of patients with arthritis, chorea, carditis or arthralgia as defined in the text. The overlaps of the circles contain patients with two or more of these properties. Patients with severe carditis are shown as a smaller circle (or subset) within the carditis group. The group with arthralgia only and no overlap of other features does not fulfill diagnostic criteria for rheumatic fever and is shown with the dashed outline. (Such patients were excluded from this investigation.) Each of the various subsets indicated in these demarcations thus contains patients with different clinical features of acute rheumatic fever. Each denominator shows the number of patients initially present in that subset and the numerator shows the number with residual rheumatic heart disease, alive or dead, at the last follow-up examination an average of 8 years later. As seen in the diagram, residual rheumatic heart disease did not appear in any of the four subsets of patients who were free of carditis initially, and had its highest rate of persistence in the subset of patients with severe carditis. Other relationships are further described in the text.

Table V Arthropathic manifestations of the index attack and residual heart disease in patients with possible or mild carditis

Manifestations	Patients with		Total
	First attacks	Recurrent attacks	
Joint symptoms (arthritis or arthralgia)	21/88 (24)	40/67 (60)	61/155 (39)
No joint symptom	7/10 (70)	14/20 (70)	21/30 (70)
Total	28/98 (29)	54/87 (62)	82/185 (44)

*Denominator is the number of patients in each category; numerator is the number with residual rheumatic heart disease. Numbers in parentheses represent percentages.

Thus at both extremes of the carditic spectrum—no carditis or severe carditis—residual heart disease seemed to be unrelated to the number of previous rheumatic attacks. In patients with possible or mild carditis, however, the valvular damage seemed to be fixed more permanently after a recurrent attack than after a first attack.

2. General Clinical Features. Table IV also demonstrates that cardiac prognosis was affected by factors other than the number of antecedent rheumatic attacks. The absence, presence, or severity of arthropathic and choreic manifestations had significant correlations with residual heart disease.

The features involved in these complex relationships are illustrated in the Venn diagram of Fig. 1, which is confined to the 271 patients with first attacks of rheumatic fever. The diagram demonstrates the specific sets and the overlapping of different clinical properties that distinguish the patients who comprise the spectrum of rheumatic fever. In each distinct subset of patients with different properties, the numbers show how many patients had that property initially and the percentage who had residual heart disease. In the zone of patients outside the carditis circle, none had residual heart disease. Within the carditis circle, the greatest amount of residual heart disease was in patients with severe carditis. Other distinctions within the groups of different arthropathic severity are further described below. Because of the relatively small numbers in each of the many clinical categories cited in Table IV and in Fig. 1, and because prognostic correlations (as indicated in the previous section) are best assessed in patients with possible or mild carditis, we have combined certain groups from Table IV and Fig. 1 for the analysis given in Table V.

Table V is confined to patients with possible or mild carditis in their (first or recurrent) index attacks. The subsets of patients have been combined according to the presence or absence of arthropathic manifestations during the acute attack, regardless of the presence or absence of chorea. The occurrence of residual heart disease is then cited for each category. In patients with first attacks or with recurrences, the patients with joint symptoms had less residual heart disease than did those with no arthropathic manifestations. In patients with recurrent attacks, the difference was not significant (60 vs. 70 per cent). In patients with first attacks, however, the difference (24 vs. 70 per cent) was statistically significant at $P < 0.01$ ($\chi^2 = 7.3$).

Thus, the earlier data presented here and elsewhere[4] indicated an inverse relationship between the severity of arthritis and carditis during acute attacks of rheumatic fever. The results just cited suggest a more lasting aspect of that relationship for patients with comparable degrees of possible or mild carditis in first rheumatic

attacks heart disease after the acute attack is much more likely to persist in the absence than in the presence of concomitant arthropathy

3 Manifestations of Acute Carditis (Table VI) In Table VI the types of murmurs and severity of carditis in the acute attacks are correlated with the occurrence of residual heart disease In each category of acute cardiac involvement patients with recurrent rheumatic attacks had more residual heart disease than did those with first attacks Among these categories however several distinct prognostic gradations may be noted

a The patients whose heart disease was most likely to disappear were those who had mitral systolic murmurs only In the group with first attacks and with definite carditis residual heart disease persisted in only 5 (24 per cent) of 21 such patients As noted earlier and elsewhere however some of the disappearances of heart disease may have been due to changes in diagnostic criteria rather than to improvement in cardiac status

b The frequent disappearance of noises considered to be solitary mitral diastolic murmurs was also a change attributable more often perhaps to auscultation than to cardiac valvular alterations In the records of the index attacks of these patients apical diastolic murmurs had been recorded as either mid-diastolic or presystolic Both these designations refer to entities of great acoustic subtlety A long physiologic third heart sound is easily confused with a mid-diastolic murmur a physiologically split first sound may be mistaken for a presystolic murmur [11] In the absence of standardization of the auscultatory techniques of the physicians who initially examined the patients it is possible that some or many of these mitral diastolic murmurs were really innocent noises that had received a pathologic interpretation Their later disappearance may then have represented changes in physiology or in auscultatory interpretation rather than true improvement of a damaged valve

c Patients with murmurs of both the

Table VI Types of murmur severity of carditis and residual heart disease after initial and after recurrent attacks of acute rheumatic fever

Types of murmur	Patients with first attacks				Patients with recurrent attacks			
	Possible carditis	Mild carditis	Severe carditis	Total	Possible carditis	Mild carditis	Severe carditis	Total
Mitral systolic only	1/16 (6)	4/18 (27)	1/3 (33)	6/37 (16)	2/11 (18)	4/7 (57)	3/4 (75)	9/2 (41)
Mitral diastolic only mitral systolic questionable or absent	0/5 (0)	2/10 (20)	2/3 (67)	4/18 (22)	1/2 (50)	7/13 (54)	5 7 (71)	13/22 (59)
Mitral systolic and diastolic no aortic diastolic	0/3 (0)	6/15 (40)	12/13 (9)	18/31 (58)	0 1 (0)	8 13 (62)	10 1 (83)	18/26 (69)
Aortic diastolic with or without aortic systolic no mitral murmur	0/5 (0)	7/14 (50)	——	7/19 (37)	0/1 (0)	1 15 (80)	——	1 /16 (75)
Aortic diastolic and mitral murmurs	——	8/12 (67)	11/1 (92)	19/ 4 (79)	——	20/24 (83)	21 21 (100)	41/45 (91)
Total	1/29 (3)	27/69 (39)	26/31 (84)	54/129 (4)	3/15 (20)	51/7 (71)	39 44 (89)	93/131 (71)

Th [illegible] for the possible card[illegible] type of [illegible] but [illegible] or [illegible]

Den[illegible] number of pa[illegible] in each category [illegible] heart disease al[illegible] Numbers [illegible] per cent

aortic and mitral valves were the least likely to lose their evidence of cardiac damage Residual heart disease remainded in 79 per cent of such patients after first attacks and in 91 per cent after recur rences

d Patients with systolic and diastolic mitral murmurs were much more likely to retain evidence of heart damage than were those with only mitral systolic or only mi tral diastolic murmurs

Thus these data demonstrate that heart disease was more likely to persist if two valves were involved rather than one and if the murmur in an involved valve was diastolic as well as or rather than systolic

4 Other Cardiac Features

a Pericarditis (Table VII) Table VII shows the occurrence of pericarditis in the index attacks of the entire population and correlates the concomitant acute cardiac involvement and the residual rheumatic

Table VII Residual heart disease in relation to severity of carditis and occurrence of pericarditis in acute attacks of rheumatic fever

Occurrence of pericarditis	*Initial cardiac status*				*Total*
	No valvular involvement	*Possible valvular involvement*	*Mild carditis*	*Severe carditis*	
With pericarditis	0/? (0)	1/2 (50)	(1)2/7 (79)	(1)9/11 (8?)	(1)12/22 (55)
Without pericarditis	0/1?9 (0)	3/42 (7)	( )76/134 (57)	( )56/64 (88)	( )135/419 (32)
Percentage of patients in this category who initially had pericarditis	1	5	5	15	5

Denominator [illegible] the number of patients [illegible] each category [illegible] the number of patients with residual rheumatic heart disease [illegible] or dead Numbers in parentheses are percentages Superscript figures [illegible] the number of patients dead of rheumatic heart disease

Table VIII Residual rheumatic heart disease in relation to severity of carditis and occurrence of prolonged P R interval in acute attacks of rheumatic fever

Occurrence of prolonged P R interval	*Initial cardiac status*				*Total*
	No valvular involvement	*Possible valvular involvement*	*Mild carditis*	*Severe carditis*	
Present	0/55 (0)	2/14 (14)	( )25/43 (58)	(1)21/?4 (83)	( )48/136 (35)
Absent	0/1?6 (0)	2/30 (7)	( )53/98 (54)	(1)44/51 (86)	( )99/305 (32)
Percentage of patients in this category who initially had prolonged P R interval	30	32	30	3?	31

Denominator [illegible] the number of patients [illegible] each category [illegible] the number of patients [illegible] residual rheumatic heart disease [illegible] Numbers in parentheses are percentages Superscript figures in parentheses are the numbers of patients dead of rheumatic heart disease

heart disease The data provide an excellent example of the distortions that can enter clinical reasoning via inappropriate statistical analysis Residual heart disease appeared in 12 (55 per cent) of 22 patients with pericarditis and in 135 (32 per cent) of the 419 patients without pericarditis This difference is statistically significant at P < 0 01 (χ = 7 6) but is clinically meaningless

As shown in Table VII pericarditis initially occurred in 5 per cent of the entire population Pericarditis was particularly likely to appear however in patients with severe carditis and most of its other occurrences were in patients who also had other initial evidence of cardiac damage Of the 22 patients with pericarditis 20 (91 per cent) initially had other evidence of cardiac involvement as compared with 240 (57 per cent) of the 419 patients who had no pericarditis

When the occurrence of residual heart disease (or of early death) is analyzed in the four comparable cardiac categories there are fluctuations in percentages due to the small numbers of patients with pericarditis in certain categories but no significant differences in residual heart disease are found among patients with and without pericarditis

These data demonstrate therefore that pericarditis is most likely to occur in patients with acute rheumatic disease who simultaneously have other evidence of severe cardiac involvement The occurrence of residual heart disease (or of early death) however depends on the involvement of valves and the size of the heart and is not influenced by the pericarditis per se

b Prolongation of P R interval (Table VIII) In contrast to pericarditis a prolonged P R interval initially occurred with equal proportions among all categories of acute cardiac involvement This electrocardiographic abnormality as shown in Table VIII was present in 136 (31 per cent) of the total population of 441 patients and appeared during the acute attacks in 30 to 32 per cent of all four cardiac subgroups regardless of the severity or absence of cardiac involvement

Residual heart disease was present in 35 per cent of the patients *with* and *in* 32 per cent of the patients without prolongation of P R interval Among the four initial categories of cardiac involvement the occurrence of residual heart disease depended on the severity of the involvement and was essentially unaffected by the presence or absence of a prolonged P R interval

These data demonstrate that prolongation of the P R interval is *not* a useful guide either to the occurrence of clinically discernible carditis in an acute attack of rheumatic fever or to the ultimate cardiac prognosis The abnormality represents altered electrical conductivity rather than histopathologic damage and is probably often due to currently unidentified chemical products that affect conduction of the cardiac impulse in the poststreptococcal inflammatory state

Discussion

Long term studies of the outcome of rheumatic fever have suffered from several kinds of defects in investigative methods

1 In many older studies the initial diagnosis of rheumatic fever was equivocal uncertain or erroneous in numerous patients This problem was particularly prevalent before the uniform use of the Jones diagnostic criteria[4] and before the availability of modern laboratory and catheterization procedures for detecting lupus erythematosus *rheumatoid arthritis* congenital heart disease sickle cell anemia and other disorders that can masquerade as rheumatic fever by fulfilling the Jones criteria

2 In some studies the patients were initially examined at many different medical centers with unstandardized techniques of examination and interpretation In such studies and in others performed at single centers uniform written criteria were often employed but the criteria were either inadequate for certain acoustic al or roentgenographic distinctions or else the application of the criteria in direct examination was not calibrated among the many different examiners[8] In one recent large scale cooperative study[11] for example such problems were particularly evident in the analysis of systolic murmurs which were assessed primarily by loudness only and of diastolic murmurs which showed different rates of prevalence at diff institutions

3 The follow up examinations of many previous studies were performed under various handicaps (a) In most situations asymptomatic patients were examined no more than once yearly and often less frequently Consequently when changes were found in cardiac status the examiners could not decide whether to attribute the changes to insidious cardiac alterations to differences in auscultatory interpretation or to subclinical recurrences of rheumatic fever (b) When the population was a group of patients followed at many *different* medical centers the examiners auscultatory interpretations were not compared or standardized when the population was followed at a *single* medical center the investigators did not use objective blind techniques or rigorous interpretive criteria for the examinations In one major study[11] that reported the final status of 100 per cent of the original 1 000 patients the investigators often had to rely on reports from distant unstandardized examiners for the follow up data of patients who had moved to other localities

The first and third of these types of defect have been essentially eliminated in the present study The population was diagnostically pure in that all patients unequivocally fulfilled the modified Jones criteria and the group had been previously freed (by appropriate tests) of patients initially suspected of rheumatic fever but then found to have lupus erythematosus or other masquerading diseases The subsequent examinations were performed at monthly or bimonthly intervals with accurate techniques for detection of intercurrent streptococcal infection and of rheumatic inflammation All follow up examinations were performed at the same clinic and by multiple examiners whose use of objective procedures detailed acoustical descriptions and rigorous interpretive criteria had improved the precision uniformity and calibration of the auscultatory process

The present study could thus eliminate major deficiencies of previous investigations in the selection of population and in follow up procedures but it shares with older studies the second type of defect varied techniques of examination for the acute attack This defect is inevitable and irremovable in studies of the type performed here The ecology and incidence of rheumatic fever are such that the observers of a single institution cannot see a statistically large enough number of acute attacks at their onset To assemble a large number of patients in the acute phase of this illness a single institution would have to combine the data of many different years of observation In such a noncontemporaneous grouping the possible distortions introduced by temporal changes in the disease itself in the type of population and in different examiners or examination techniques would negate the advantages otherwise gained An alternative approach to this problem is a cooperative type of study which obtains large numbers of contemporary patients who are seen examined and followed at different institutions In such a study the absence of direct calibration among the different examiners introduces the difficulties already cited in the interpretation of the initial and follow up data In the present work a large number of essentially contemporary patients were all followed by a single institution to which they had been referred *after* the immediate onset of the acute rheumatic attack The examinations of the initial stages of those attacks could therefore not be performed with uniform scientific precision Nevertheless it seems unlikely that any *single* type of observational bias was present in the acute examinations because the patients had come from so many diverse sources and because the acute findings agree consistently with those in the more closely examined population[4] whose data were used for comparison

Thus the necessary disadvantages of the way the population was initially assembled seem greatly outweighed by the opportunity for the precision of follow up techniques subsequently employed Moreover any existing deficiencies in the acute clinical data do not affect the most significant conclusion of this investigation which is that rheumatic heart disease does not seem to develop in patients initially free of it A few patients may possibly have had significant murmurs that escaped detection during portions of the acute attacks observed elsewhere or at Irvington House If such unheard murmurs had occurred

often the phenomenon might explain the development of some heart disease that appeared *de novo* Yet no such new heart disease developed If the subsequent auscultatory criteria were too lax some new heart disease might have been spuriously diagnosed at follow up examinations because of pathologic interpretation of physiologic noises that had previously been more accurately diagnosed Again the absence of *de novo* heart disease rules out this type of error

The errors that may exist in the present study are probably of two types (a) The initial auscultatory criteria of the referring physicians may have been too lax Patients may have received an organic diagnosis for noises that were really innocent The heart disease that later disappeared in such patients would thus be a triumph not of cardiac repair but of physiology time or improved auscultatory interpretation (b) The subsequent examining criteria in the clinic may have been too rigorous In particular mitral valve deformity may actually be present in some patients whose apical systolic murmurs were regarded as being nonrheumatic because the murmurs did not fulfill all the sonorous criteria which we required for mitral regurgitation The mitral valve may also be deformed in other patients with isolated mid-diastolic noises that we regarded as physiologic third heart sounds rather than as organic murmurs

In the absence of complete anatomic verification in all patients the validity of our rigorous auscultatory criteria cannot be proved The major existing data to support the accuracy of these criteria are of two types (a) In all patients found to have mitral regurgitation at necropsy or operation the lesion had been correctly identified by the auscultatory standards that we employed and (b) the systolic murmurs deemed to indicate no rheumatic heart disease by our rigorous criteria have often later disappeared and have not been followed in any patient by the development of cardiac symptoms cardiac enlargement or significant ECG abnormalities in the observation period For the apparently physiologic systolic murmurs of the many asymptomatic patients who have had a clinically benign course in this project it does not seem justifiable to perform all the routine catheterizations or angiography that would be required to verify the absence of organic heart disease The exact confirmation or refutation of our auscultatory diagnostic criteria must therefore come from continued long term observation

A separate issue that needs clarification is the reason for the relatively benign course seen in so many of these rheumatic patients About two thirds of the group have no residual rheumatic heart disease and most of those with objective signs of cardiac damage have no clinical symptoms or decompensation Is the relative lack of cardiac difficulties in this population attributable to the use of antistreptococcal prophylaxis or is it a feature of rheumatic fever that was first clearly identified in patients receiving prophylaxis? Do patients free of carditis remain free of rheumatic heart disease because of better modern auscultatory methods or is it because antistreptococcal prophylaxis has kept them either from developing insidious cardiac deterioration or from acquiring heart disease in recurrent rheumatic attacks?

Our current belief is that prophylaxis is an indirect concomitant of these findings and not their cause The main contribution of prophylaxis to these data was its creation of the need for large scale clinical investigations of the comparative effectiveness of different prophylactic agents These investigations of prophylaxis required assembly and maintenance of a large population of patients examined repetitively at a single institution for detection of streptococcal infections and rheumatic recurrences At the same time however the repetitive examinations provided the opportunity for improving the quality objectivity and precision of clinical observation techniques With this improvement the current cardiac findings were observed

Prophylaxis was thus reponsible for the situation in which better methods of clinical investigation previously unused or unavailable could be applied to studies of rheumatic cardiac sequelae It seems unlikely that prophylaxis per se was the cause of these result Although prophy

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Diuretic therapy Part VII Spironolactone

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The synthesis of spironolactone in 1957 made available a new and interesting compound which was later found to have potent physiologic activity. A chemical analogue of aldosterone the molecule in large part duplicates the structure but not the clinical effect of the adrenocorticosteroids. Its mode of action is considered to be a competitive inhibition of mineralocorticoids at effector end organs including the renal tubules and the salivary and sweat glands. It has been found to inhibit the sodium retaining and potassium excretory effects of aldosterone desoxycorticosterone and hydrocortisone (but not the other physiologic actions of hydrocortisone). Spironolactone† has not been found to affect the excretion of 17 ketosteroids or 17 hydroxycorticoids but it can reverse all the known actions of aldosterone. Since the secretion of aldosterone is known to be stimulated by hyperkalemia hyponatremia and by a decreased effective blood volume (and hence by the resultant effect of thiazide and mercurial diuretic treatment) the physiologic actions of this peripheral aldosterone inhibitor have been somewhat difficult to study and some conflicting results have been reported. In general the drug appears to be pharmacologically inactive in the absence of aldosterone or similar substances. Clinically it is used in the more or less refractory edematous states in which the mineralocorticoid substances contribute to the abnormal retention of fluid. These states include nephrosis some cases of chronic congestive heart failure cirrhosis with ascites and occasional cases of idiopathic edema.

The thiazides and spironolactone appear to act synergistically. The former agents probably retard sodium and water reabsorption predominantly in the proximal convoluted renal tubule whereas spironolactone accomplishes the same action (by inhibition of aldosterone) primarily at the site of the distal convoluted tubule. Hence more sodium will appear in the distal tubule because of absorption block and less potassium will be secreted and exchanged for these blocked sodium ions.

Where the role of increased aldosterone was uncertain spironolactone has been administered with the resultant successful stimulation of diuresis in some patients. Hyperaldosteronism reported by some to be present in this same situation may be partly due to previous diuretics administered in an effort to deplete sodium or in other instances to the reduced hepatic destruction of aldosterone (cirrhosis or

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† [illegible] Aldactone-A (25 mg tablets) [illegible] Aldactone (100-mg tablets) [illegible]
[illegible]

cardiac congestion of the liver) Whatever the role of aldosterone it is clear that spironolactone is less effective in congestive heart failure than in other states clearly associated with an increased secretion of aldosterone such as in the nephrotic syndrome or cirrhosis of the liver Also it has been found to exert a natriuretic chloruretic and diuretic effect in cirrhotic patients even without the presence of edema or ascites

Clinically spironolactone should rarely be the first and only drug used for treatment It usually is reserved for those cases which prove to be refractory to the commonly used diuretics When spironolactone is used alone diuresis may be minimal reaching a maximum on the third day of treatment and then decreasing if administration of the drug is continued The action of spironolactone persists for 2 to 3 days after discontinuance of the drug The usual dosage is 25 mg administered orally every 6 hours but an increase in diuresis in some cases has been reported using up to 300 mg daily In general patients treated with a dosage beyond this amount manifest no additional diuretic effect Employed as the sole agent in the treatment of ascites it is rarely effective since most of the sodium is reabsorbed proximal to the site of action in the distal tubule Studies reveal that spironolactone is more efficient during a low rather than during a high intake of sodium whereas a low intake of potassium will inhibit or diminish natriuresis Nevertheless spironolactone will not promote a loss of potassium but on the contrary may result in hyperkalemia (even before adequate diuresis) possibly even within 5 to 7 days of beginning therapy No evidence of a direct effect on the level of blood ammonia has been noted Since the administration of spironolactone may elevate an already elevated blood urea nitrogen it should not be used to induce diuresis in patients with moderately or greatly increased blood urea nitrogen

The most widely employed practical and effective therapeutic combination is spironolactone 25 to 50 mg every 6 hours plus a thiazide (such as chlorothiazide 500 mg every 12 hours) Occasionally a mercurial diuretic is substituted for the thiazide Usually a greater natriuresis is induced than the sum of that obtained with either agent used alone With this therapy diuresis may be induced in patients resistant to thiazide therapy alone

Spironolactone will not prevent the side effects of thiazides (on carbohydrate metabolism or retention of uric acid) but combined therapy will not usually induce hypokalemia or digitalis toxicity Not infrequently resultant hyperkalemia and hyponatremia may be seen during treatment

A lack of response to a spironolactone thiazide regimen suggests a poor prognosis Treatment should be discontinued if no response is noted after a brief trial period Cirrhotic patients who were found to be refractory to spironolactone thiazide or a mercurial plus a steroid and a low sodium diet have shown evidence of severe hepatic failure with an extremely poor prognosis One must be alert for the possible development of hyperkalemia acidosis hyponatremia or uremia Other side effects which have been seen during the administration of spironolactone include a maculopapular or erythematous rash mental confusion drowsiness ataxia gynecomastia facial hirsutism epigastric distress and muscle cramps

Spironolactone both alone and together with a thiazide diuretic has also been used in the treatment of hypertension Here again natriuresis may be induced without the development of hypokalemia The maximal hypotensive effect with spironolactone may not be seen until after 1 to 3 weeks of treatment Increased urinary aldosterone may be noted during the administration of spironolactone Hypertension associated with primary aldosteronism has been reported to respond to spironolactone after 2 to 4 weeks of treatment but in general hypertension associated with secondary aldosteronism responds rather poorly Hence lack of blood pressure response to the drug papilledema and low serum sodium favor a diagnosis of malignant or severe hypertension and not the primary type of hyperaldosteronism The use of spironolactone for distinguishing primary from secondary aldosteronism has been studied in the following way If hyperaldosteronism is suggested by clinical

and biochemical methods supplementary potassium (at least 80 mEq.) is given daily for 5 days. If the serum potassium does not become normal, then spironolactone, 200 mg daily, is added to a diet containing normal amounts of sodium and potassium for 4 days. Serum potassium should now rise to within normal limits if primary aldosteronism is present.

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Annotations

Cystic myxomatous degeneration of the popliteal artery

Cystic myxomatous degeneration of the popliteal artery is a rare cause of intermittent claudication in young adults. The first case was described by Ejrup and Hiertonn who noted the similarity of their findings to those in a case in which the external iliac artery was involved. However Hiertonn later collected 3 more cases involving the popliteal artery, and these and the original cases were described by Hiertonn, Lindberg and Rob. The cardinal features common to these cases were described by Hiertonn and Lindberg[7] as (1) occurrence in young males, (2) sudden onset with cramps in the calf, (3) development of typical intermittent claudication, (4) presence of a localized stenosis and/or occlusion of the popliteal artery, (5) absence of generalized arterial changes, (6) formation of intramural cyst between media and adventitia compressing the arterial lumen, (7) cyst contents of gelatinous material under tension, (8) cyst wall lined by flattened cells, and (9) structure of cyst wall suggestive of mucinous degeneration.

Since this description 7 more cases of the disease involving the popliteal artery have been described and additional cases are mentioned by Sutton[10] and Eastcott. The description of additional cases has made necessary a revision of the cardinal features as originally delineated.

The similarity of the clinical features in these cases and the consistency with which the popliteal artery only has been involved seem to indicate that cystic myxomatous degeneration of the popliteal artery is a definite disease entity with a characteristic pathology.

All the patients have been adults between the ages of 24 and 50 years. The condition is more common in males and to date only 2 cases in women have been described. The males have mostly been manual workers and several have been employed in heavy industry.

Inflammation, hemorrhage, and trauma are possible etiological factors which have been considered. Dense periarterial adhesions are common and in one case infiltration with inflammatory cells was present histologically. Hiertonn and Lindberg[7] and Holmes[8] believed that these changes were secondary and excluded inflammation and hemorrhage on the basis of their histologic and biochemical findings.

In the absence of a definite traumatic incident most authors have accepted repeated minor trauma as being the most important etiological factor. If this is so it seems strange that the condition is so rare especially in the groups which would be most at risk, such as cyclists, athletes, etc. It would seem that there are other etiological factors of importance in the pathogenesis of the disease as yet unknown.

The onset has nearly always been sudden; the patient has been smitten with cramping pain in the calf, usually while walking quietly rather than during extreme effort. The initial sudden pain is associated with symptoms and signs of ischemia such as pallor, coldness, numbness, and paresthesiae in the involved limb. The acute symptoms gradually give way to typical intermittent claudication and the signs of acute ischemia pass off. Pulses in the ankle are present in all patients at this stage unless secondary thrombosis of the involved segment of popliteal artery has supervened. These clinical features are not diagnostic. The diagnosis is likely to be an arteritis of, for example, the Buerger type if the patient is a young male. In the older patient an early onset of atheromatous occlusion may be considered. However Ishikawa found that in their patients with incomplete arterial obstruction and normal findings at rest, full flexion of the knee produced pallor, coldness, and absence of pulses in the ankles. It may be that this sign will be of diagnostic value when the block is incomplete. Eastcott[4] suggests that the condition should be considered in all young subjects who are non-smokers, especially if in addition, as in his case, a bruit is present over the popliteal artery.

The sudden onset of symptoms is difficult to explain since an intramural mucin-containing cyst is unlikely to appear acutely. The sudden onset cannot be associated with secondary thrombosis supervening on asymptomatic cyst since the sudden onset was also common to cases of incomplete obstruction. However a sudden minute intramural dissection might give rise to acute spasm, thereby producing ischemic symptoms, this dissection then being followed by the development of an effusion which subsequently becomes mucoid.

Arteriography may show a localized stenosis of variable severity or a segmental occlusion in the upper part of the popliteal artery. A stenosis appears as a smooth filling defect, usually unilateral and suggestive of extrinsic pressure. The artery is not, however, deviated from its course. Occasionally the stenosis shows an hourglass deformity. The other

vessels appear to be normal and a collateral circulation does not develop presumably because arterial insufficiency is only present intermittently. The degree of stenosis may vary with posture as Ishikawa and associates[10] have beautifully demonstrated with lateral arteriograms of the knee. They showed that full flexion caused accentuation of the stenosis together with a change in the normal U shape of the flexed artery to an M shape presumably due to the popliteal artery being kept locally more rigid by the encircling cyst.

Once the occlusion has become complete there may be no specific arteriographic or clinical features to suggest the diagnosis, which is made only at exploration. However Anderson and associates[1] demonstrated a tapering of the refilled artery immediately below the occlusion, which when present is very suggestive of the condition. The appearance is due to compression of the arterial lumen by the lower part of the cyst. The occluded segment is usually short and a good collateral circulation develops.

The cyst itself is either unilocular or multilocular and contains viscid mucus. It may or may not be lined by a layer of flattened cells. It is situated within the outer layers of the media or between media and adventitia. In two of the reported cases complete enucleation of the cyst was performed, the specimen resembling a myxoma or ganglion, whereas in other cases including our patient this would not have been possible. It may be that the myxomatous type of case represents a later stage in the pathogenesis with the development of a definite lining to the cyst wall.

The management of the condition depends on whether secondary thrombosis has occurred. In the absence of this complication enucleation of the cyst whenever possible or incision and evacuation of its contents is the treatment of choice. This will result in a return of normal pulsation and blood flow. When secondary thrombosis has occurred the treatment of choice lies between excision and grafting and incision of the cyst and coincidental thromboendarterectomy. Grafting has been done in all but one of the reported cases and no long term follow up is available. The patient of Tytgat and associates[14] suffered a recrudescence of symptoms after 4 months suggestive of thrombosis of the graft whereas Eastcott[5] has recently quoted a 3 year follow up of a previously unreported case in which there was full function of the limb and no symptoms. This patient was treated by evacuation of the cyst and simple suture reconstruction of the artery. In view of previous experience in grafting the popliteal artery[4] it is probable that thromboendarterectomy is the better method of treatment.

It is now possible to give a reasonably accurate description of the cardinal features of the disease although as yet several questions remain unanswered, notably the exact pathogenesis and the late prognosis. These features may be summarized under the usual headings as follows:

1 *Etiology* This is a condition of unknown pathogenesis which occurs principally in young adults employed in heavy manual work. Females and those in lighter occupations are occasionally affected.

2 *Clinical picture* There is a sudden onset of cramping pain in the calf followed by the development of typical intermittent claudication. Signs of ischemia are present although sometimes only on exertion and may be exacerbated by full flexion of the knee. Arteriography shows a smooth walled stenosis or a complete block in the popliteal artery with an otherwise normal arterial tree.

3 *Pathology* A unilocular or multilocular cyst is present within the wall of the popliteal artery compressing the lumen.

4 *Treatment* In most cases evacuation of the cyst is sufficient. Thromboendarterectomy or excision and grafting may be necessary when secondary thrombosis of the lumen has occurred.

5 *Prognosis* The short term prognosis after operation is excellent but no long term follow up reports are available at present.

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A simple bedside technique for timing the cardiac cycle

There are occasions when it is difficult even for an able clinician to distinguish systole from diastole and the first sound from the second heart sound by simple auscultation. All physicians have had difficulty at times, even after careful examination, in deciding whether a murmur is systolic or diastolic or which of the heart sounds is the first and which is the second. This difficulty was experienced by one of us (S. A. L.) about 35 years ago. At that time a patient was seen at the Peter Bent Brigham Hospital who had been followed for several years by Dr. William S. Thayer in Baltimore. She then moved to Boston and was under the care of Dr. Henry A. Christian. She was also seen by one of us (S. A. L.) on several occasions at Dr. Christian's request. She was always regarded as having some form of congenital heart disease. All observers described a moderately loud heart murmur, systolic in time. During those earlier years the exact anatomic diagnosis of congenital heart disease was not so accurate as it is at present. Although she was regarded by all those who attended her as having a congenital lesion, possibly a ventricular septal defect, on one occasion while one of us was listening to the heart the patient happened to take a deep breath. The heart slowed as a result, as commonly occurs, and a few slow beats were heard. To the great surprise of the listener, the murmur that previously had always been considered to be systolic in time by all observers lengthened and practically filled the few long diastolic pauses that resulted from the sinus slowing. It became quite clear that the murmur had been misinterpreted in time and was a diastolic rather than a systolic murmur, for the changes in the length of the cardiac cycle take place almost exclusively as a result of varying lengths of diastole and not of systole.

The confusion in timing the events of a cardiac cycle may involve the question whether a murmur is systolic or diastolic, whether an accentuated or a muffled sound is the first or the second sound, or whether a gallop or third sound is in systole or diastole. In trying to resolve such difficulties one may attempt to synchronize the auscultatory findings with a visual pulsation in the carotid artery, the apex region, or over the precordium, or with the palpation of radial, carotid, or apical beats. It is no simple matter to relate accurately the timing of sensations obtained simultaneously by visual, tactile, and auditory means. Sometimes these observations enable a physician to make a satisfactory decision. However, not infrequently, try as one may, doubt can remain and one feels impelled to take a phonocardiogram simultaneously with an electrocardiogram, which then definitely establishes the exact time relationships of the various cardiac events.

Very recently another experience occurred similar to the one described above. A 49-year-old man entered the hospital complaining of sweats, malaise, and fever. It was quickly apparent that he probably had subacute bacterial endocarditis. The spleen was palpable and the heart, although regular, showed a loud Grade 3 murmur. This mur-

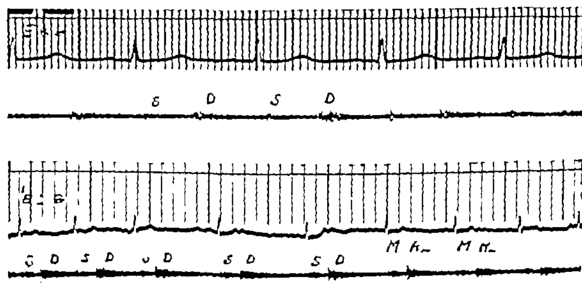


Fig. 1. *Above:* The electrocardiogram and phonocardiogram during normal breathing. *Below:* The tracings show the effect of right carotid sinus massage; note slowing of the rate. The first event after the long pause, the faint (almost inaudible) systolic murmur, and the prominent loud murmur is actually in diastole. *S*, Systolic murmur. *D*, Diastolic murmur. M_1, First heart sound. A_2, Second sound.

mur was thought to be systolic in time by the home physician who was a competent internist, by the medical intern in our hospital, and by one of us (S.V.L.). For some reason doubt arose in our minds whether this murmur was actually systolic. When the patient was asked to take and hold a deep breath, the heart slowed very noticeably and the short murmur lengthened out. It quickly became quite obvious that with the long diastolic pauses the murmur filled the entire diastole. Here again the peculiar sounds and cadence that were present made all the observers think that the murmur was systolic when in fact it was diastolic in time. These events were well displayed in the phonocardiographic tracing which was taken (Fig. 1) and which quickly confirmed the simple bedside observation. In fact, any means which might slow the heart, such as carotid sinus massage, would similarly resolve the difficulty and confusion. This simple procedure of slowing the heart would be helpful in identifying which sound is the first and which is the second and would distinguish a mid systolic gallop from a diastolic gallop. Although this maneuver has been mentioned before, little attention has been paid to it. One merely has to bear in mind that the first sound heard after a long pause must be the first heart sound and not the second, and the first interval after a long pause must be systole and not diastole. Deliberate slowing of the heart by such simple means as having the patient take a deep breath or by carotid sinus massage and focusing attention on the points just discussed may quickly clarify some otherwise mistaken or doubtful observation.

Conclusion. Occasionally it is difficult even for competent physicians to time the events of the cardiac cycle without phonocardiographic data. Temporarily slowing the heart by having the patient take a deep breath or by carotid sinus massage may quickly clarify whether a murmur is systolic or diastolic in time, would distinguish which is the first and which the second heart sound, and might differentiate a mid systolic from a diastolic gallop.

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A brief survey of the health of aged Hunzas

During the last few decades occasional interest has been expressed concerning the state of health of the inhabitants of Hunza, a small principality high in the Himalayas in the Karakorum Range north of Pakistan. Rumors have been widespread that the people in this country live astonishingly healthy lives to a ripe old age, but there has been no scientific confirmation of these rumors. Travelers, mostly tourists, have gone in very small numbers to visit Hunza and have come out with interesting observations concerning the beauty and interest of the country and the apparent good health of its inhabitants.

A few years ago the senior author (I. D. W.) was invited to make a study of the health of the Hunzas, but this was impossible at that time. The recent tour of military medical duty of the junior author (E. G. T.) in the northwest frontier province of Pakistan with headquarters in Peshawar revived interest in the possibility of making a preliminary visit to Hunza as a pilot test of exploration concerning the health and longevity of the Hunza people. Permission and support of the plan were kindly granted by Marshal Ayub, President of Pakistan, and his medical staff. With a cordial invitation from the Mir (Prince) of Hunza, a visit was paid to Baltit via Gilgit in September, 1962. An hour's flight from Rawalpindi to Gilgit initiated the journey into Hunza. A week was spent with the kind hospitality and cooperation of the Mir and his people in obtaining data on 25 aged Hunza inhabitants, and this brief note summarizes the findings.

Hunza is located at the "roof of the world"

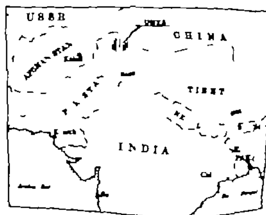


Fig. 1. Map showing location of Hunza.

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where the Himalayas reach eastward to Tibet and the rugged Karakoram Range stretches west to Afghanistan, it has borders with Chinese Turkestan (Sinkiang Province) and Afghanistan, and it lies only a few miles from India and the U.S.S.R. The final 65 miles of the trip to Baltit, the capital of Hunza, is by jeep from Gilgit over a road following the Hunza River which at many points is little more than a rocky ledge blasted from a sheer cliff 2,000 feet above the floor of the Hunza Valley.

In this mountain-high Himalayan kingdom there are more mountain peaks rising above 20,000 feet than there are peaks over 10,000 feet in all of the Alps. Agriculture is the Hunzas' primary means of livelihood and forms the basis for their unhurried, methodical way of life. The rocky, terraced soil of Hunza is irrigated with water from melting glacier by a system of canals which constitutes an engineering feat. All the available land in Hunza is cultivated and utilized for agricultural purposes. For this reason the grazing of goats and cattle is not feasible or practicable. This accounts for the absence of milk and milk products from the Hunza diet.

Hunza has 25,000 inhabitants. Theirs is a Spartan diet, the mainstay of which are fruits and nuts; vegetables and grains (barley, wheat, and millet) make up the balance of the dietary intake. Meat, primarily mutton, is eaten only once or twice during the year, usually during the festival month of December.

Twenty-five male inhabitants of Hunza were studied; they were between 90 and 110 years old on fairly good evidence. Determinations of blood pressure were within the range of 120 to 150 mm. Hg systolic and 70 to 90 mm. Hg diastolic. Determinations of blood cholesterol, carried out at the U.S.A.F. Dispensary laboratory at Peshawar, West Pakistan, were found to range between 150 and 160 mg. per cent in 6 individuals, between 160 and 170 mg. per cent in 9, and between 170 and 180 mg. per cent in 10. Electrocardiograms, taken with a portable, battery-operated Sanborn Cardiette, were interpreted by the medical staff at the U.S.A.F. Dispensary at Peshawar as showing no evidence of cardiomegaly or coronary heart disease.

The findings of normal blood pressure, normal blood cholesterol levels, and normal electrocardiographic patterns among 25 long-lived inhabitants of a remote valley in Pakistan, where dietary intake involves little, if any, meat, milk, or fat, and where the tempo of life is deliberate and unworried, suggest a correlation between the Spartan diet and way of life of the Hunzas and the apparent low incidence of heart disease, especially of the coronary type.

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It is with much appreciation that we acknowledge the help afforded by the Sanborn Company of Waltham, Mass., through the donation of the battery-operated portable electrocardiograph.

Papillary necrosis: Pathology and management of the acute attack

During the years 1960 and 1961, 12 cases of papillary necrosis were encountered in which the diagnosis was established during life.

A striking feature of the illness in all 12 of these cases has been the occurrence of acute episodes of pain and pyrexia. The clinical features of these attacks have been remarkably uniform, and the syndrome has been sufficiently characteristic for a correct provisional diagnosis to be made on several occasions. A typical acute papillary necrosis attack begins with renal colic or sudden severe pain of renal distribution, and this is accompanied or followed by pyrexia, sometimes with rigors, and a severe general illness. Frequency of micturition and dysuria are usually present, and sometimes hematuria. The affected kidney is tender and may be palpably enlarged. The urine is infected by either a coliform organism or a Proteus bacillus, but the response to an appropriate antibiotic is slow or unsatisfactory.

These attacks are due to obstruction of the ureter or a major calyx by a detached papilla. It is this obstruction which accounts for the renal colic or renal distention pain with which an attack begins. Since the urine is infected, obstruction is inevitably followed by pyonephrosis. It is this pyonephrosis which is responsible for the severity of the general illness, and repeated bouts of pyonephrosis probably cause most of the severe and permanent renal damage which occurs in so many patients suffering from this disease.

Retrograde pyelograms were performed during acute attacks in 4 patients. These films have shown that pyonephrosis was present, and the process of resolution of this condition has been followed. After an attack has been in progress for some days the pyelogram has shown masses of irregular necrotic material in the kidney pelvis, with extensive cavities and sinuses extending into the renal tissue. As resolution has progressed, cavities and sinuses have closed and, finally, after some months, the picture has become indistinguishable from that of

chronic pyelonephritis unless some papillary masses have remained when filling defects provided continuing evidence of the diagnosis

This condition is a urological emergency and relief of the obstruction is required urgently

Suction drainage through a ureteric catheter[3] is an effective technique which has been used for more than 10 years in the management of patients with pyonephrosis and calculous obstruction and it has been found to be well suited to the management of papillary necrosis attacks. A ureteric catheter with one end in the kidney pelvis is not of much use as a drain when the other end is led to an open receiver but if the low negative pressure of a Wangensteen suction apparatus is applied to it then efficient drainage is provided even though the kidney may contain thick pus. This method has been employed in the management of 10 obstructive attacks in 7 of the cases in this series

Open surgery On 3 occasions open surgery has been required for the removal of papillae which caused recurring obstruction after a ureteric catheter had been removed. Operative convalescence after pyelotomy was uneventful in all 3 cases and later pyelograms have shown good function and minimal changes

Diagnosis and treatment of the acute attack Papillary necrosis with an attack of obstruction is suspected when the combination of renal colic and pyrexia is encountered or when a patient with a diagnosis of acute pyelonephritis does not respond rapidly to treatment with an appropriate urinary antiseptic

In these circumstances emergency intravenous pyelography is performed. A plain film and a film taken 15 minutes after the intravenous injection of contrast medium will usually provide sufficient information. Abdominal compression need not be used. If no calculi can be seen and the affected kidney shows signs that suggest obstruction then the passage of a ureteric catheter is indicated. If pus or purulent urine is discovered in the kidney then suction drainage is applied and if it is not in use already an appropriate antibiotic in full dosage is administered. When the attack has been controlled and the patient is apyrexial then retrograde pyelography should be performed before the ureteric catheter or catheters are removed. The kidney pelvis is filled by gravity with a head of no more than 18 inches in order to avoid any risk of spreading infection or causing pyaemia. If the pelvis of the kidney appears to be clear of necrotic material the catheter may be removed. If large filling defects are present the question of surgical removal will have to be considered

The indication for open surgery has been that of necessity. It is thought that when pyonephrosis occurs because of an obstructing papilla the obstructing protein mass is eventually digested by ferments in the pus which bathes it and this results in spontaneous relief of obstruction after a varying time but during this time serious damage is done to the kidney. If the obstruction is relieved by a ureteric catheter and suction then digestion of the papillae commences so that residual protein masses now require operative removal. If this is not done the obstructive attack recurs as soon as the catheter is removed. The objections to surgery are that additional papillae may slough off at any time; there is no way of telling when or whether this will occur, and repeated open operation is not desirable and may not be feasible. Moreover at operation it is not possible to be certain that all necrotic papillae have been removed

It would seem from intravenous pyelograms and renal function tests on these cases and from reports in the literature especially from Sweden that the loss of papillae of itself causes remarkably little impairment of renal function. On the other hand repeated attacks of obstructive pyonephrosis undoubtedly cause extensive and permanent damage and it seems not unreasonable to hope that early and adequate treatment of these obstructive attacks will improve the prognosis in cases of this disease

It is suggested that some cases which are regarded as instances of recurring pyelonephritis with rapid progress may in fact be cases of papillary necrosis and in such cases serious renal damage may be prevented by the method suggested

It is believed that there is no general realization of the nature or the gravity of these obstructive attacks

Addendum Since this paper was written there have been 5 more cases of removal of necrotic papillae from the kidney. In one case a papilla was left behind (or another sloughed off) and further operation was needed 10 days later

These cases have now been followed for 18 months to 2½ years and the disease appears to have become quiescent and the patients remain well. It was feared that further obstructive attacks might occur and present a difficult surgical problem and indeed this may yet occur but so far no patient in whom removal of necrotic papillae from the kidney has been complete has suffered further obstructive attacks and recovery of function has been satisfactory. A low grade urinary infection persists however in most cases and in only one case so far has the urine been rendered sterile

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Book review

Le Coeur Pulmonaire Chronique. By A. Tournaire, M. Tartulier, J. Blum, F. Devrieux and R. Guyot. Paris, 1964, L'Expansion Scientifique Française, 212 pages.

In five chapters this book describes common and distinct features of chronic cor pulmonale (CCP) as engendered by five pathologic entities, namely, generalized obstructive pulmonary emphysema, fibroses of all kind, kyphoscoliosis, obesity and recurrent pulmonary embolism—all ending in classic right ventricular failure. Each chapter encompasses clinical data, pathophysiologic mechanisms, as well as cardiopulmonary function studies and therapeutic considerations dealing with those five etiological headings. Due attention is paid, however, to the intricacies commonly observed in the same patient, especially in the case of pulmonary fibroses between the two main factors at play: alveolar hypoventilation and alveolar-capillary block. This study has been partly based upon a limited number of personal cases thoroughly investigated by these authors from Lyon, France.

Chapters devoted to pulmonary fibroses and obesity are quite good. By contrast, the space alloted to CCP and emphysema appears to be small (38 pages), despite the author's own statement that "among all pulmonary diseases prone to produce CCP, emphysema stands by far the most frequent." Furthermore, this section is somewhat weak in several respects. The very causes of emphysema have not even been alluded to, nor has the puzzling fact been stressed that scarcely 25 per cent of the patients with emphysema develop cor pulmonale. A problem challenging the most experienced clinicians has not been raised: the difficult differentiation between mere emphysematous dyspnea on exertion and *associated* painless angina ("blockpnea" as coined by Gallavardin) revealing ischemic heart disease in the same individual. The authors divide the natural history into two stages—"premonitory syndrome" and "confirmed CCP"—but they erroneously include in the first stage the clinical radiologic and electrocardiographic signs of right ventricular hypertrophy, whereas the true "premonitory" phase should be only the first link in the evolutionary chain, i.e., pulmonary hypertension *without* right ventricular hypertrophy at least discernible in vivo. We know that the natural evolution goes through three stages: pulmonary hypertension, then right ventricular hypertrophy without failure, and lastly right ventricular failure. Therapeutic considerations are open to criticism. There is no allusion to sympathomimetic agents as bronchodilators, and no mention is made of intermittent positive pressure respirators presently in general and easy use (only iron lung machines and Engstrom apparatus are praised, which are formidable weapons to be reserved for dramatic situations). Timorous recourse to oxygen therapy is reluctantly recommended, although it is known that judicious utilization of oxygen has proved to be so beneficial to these patients in relieving hypoxia (hence pulmonary hypertension), provided that due attention is paid to avoiding carbon dioxide narcosis.

The section allotted to CCP and recurrent embolism is very good, but a hint on the role possibly played by serotonin and tissue kinin in the functional component of chronic arterioconstriction is lacking. By the same token, the authors do not mention such medications as heparin and antiserotonin drugs, which might be worth trying in chosen situations, at least upon theoretical and experimental ground, as well as isoproterenol, since that adrenergic beta receptor stimulant is apt to enhance a profitable vasodilation on the pulmonary arterial tree.

The printing and illustrations are good. The style is alert and generally clear. On the whole, despite the foregoing minor criticisms and lack of original findings, this book is a good one. It will fit particularly the need of French speaking beginners in cardiology training, providing them with a type of "primer" which outlines in a satisfactory way the multifacetted subject of chronic cor pulmonale.

Author index*

J ly pp 1-144 August pp 145-290 September pp 291-434 October pp 435-580 November pp 581-722 December pp 723-862

T

U

V

W

Y

Z

Subject index*

*July pp 1 144 August pp 145 290 September pp 291 434 October pp 435 580 November pp 581 722 December pp 723-862

D